GENETIC INVESTIGATIONS IN CHRIST-SIEMENS-TOURAINE AND PAPILLON-LEFÈVRE SYNDROME IN THE EYES OF THE DENTIST

PhD. dissertation

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List of publications

Publications directly related to the subject of the dissertation

I. Ágnes Kinyó, **Péter Vályi**, Katalin Farkas, Nikoletta Nagy, Brigitta Gergely, Kornélia Tripolszki, Dóra Török, Zsuzsanna Bata-Csörgő, Lajos Kemény, Márta Széll. A newly identified missense mutation of the EDA1 gene in a Hungarian patient with Christ-Siemens-Touraine syndrome. Arch Dermatol Res. 2014 Jan;306(1):97-100. IPF: 2.708.

II. Katalin Farkas, Ekaterine Paschali, Ferenc Papp, **Péter Vályi**, Márta Széll, Lajos Kemény, Nikoletta Nagy, Zsanett Csoma. A novel seven-base deletion of the CTSC gene identified in a Hungarian family with Papillon-Lefèvre syndrome. Arch Dermatol Res. 2013 Jul;305(5):453-5. IF: 2.708

III. Nikoletta Nagy, **Péter Vályi**, Zsanett Csoma, Adrienn Sulák, Kornélia Tripolszki, Katalin Farkas, Ekaterine Paschali, Ferenc Papp, Lola Tóth, Beáta Fabos, Lajos Kemény, Katalin Nagy, Márta Széll. *CTSC* and Papillon-Lefevre syndrome: detection of recurrent mutations in hungarian patients, a review of published variants and database update. Molecular Genetics & Genomic Medicine. 2014 May:2(3):217-228.

IV. **Péter Vályi,** Katalin Farkas, Adrienn Sulák, Kornélia Tripolszki, Lajos Kemény, Katalin Nagy, Nikoletta Nagy, Márta Széll. European recurrent missense mutation in a Hungarian pedigree with Papillon-Lefevre syndrome. Fogorv Sz. 2014 Sept.: 107(3): 87-92

Publications indirectly related to the subject of the dissertation

I. **Péter Vályi**, István Gorzó, Tiina Varella, Liisi Sewón, Pekka Vallittu:. Effect of occlusal therapy with FRC splint on periodontal parameters in maintenance phase. Fogorv Szle.: 2005 Aug; 98(4):159-63. Hungarian.

II. **Péter Vályi**, István Gorzó. Periodontal abscess: etiology, diagnosis and treatment. Fogorv Sz. 2004 Aug; 97(4):151-5. Review. Hungarian.

III. **Péter Vályi**, István Gorzó, András Kocsis, Endre Kiss, Attila Tóth.. Direct application of fiber-reinforced composites in splinting in a case of periodontitis. II. Fogorv Sz. 2003 Feb; 96(1):29-32. Hungarian.

IV. **Péter Vályi**, István Gorzó. Current splinting methods in dentistry. I Fogorv Sz. 2003 Feb; 96(1):25-8. Review. Hungarian.

V. **Péter Vályi**, István Gorzó, Albert Mari: Hygiene in dentistry. I. Contamination of handpieces and dental units. Fogorv. Sz. 1999 Jun; 92(6):167-74.

VI. **Péter Vályi**, István Gorzó, Albert Mari: hygiene in dentistry II: Disinfection of dental handpieces. Fogorv. Sz. 1999 Jul; 92(7):213-8

1. Introduction

1.1. Introduction into rare diseases

Rare diseases affect only a small percentage of the population. They are defined as diseases with smaller incidence than 1:2000 (Kelsall *et al.,* 2013). However a rare disease affects nationwide only a few patients, but - due to their thousands of different types – altogether they affect a significant portion of the population. Generally little is known about these disorders compared to the common ones. They occur rarely in the practice of a dentist or other medical practitioner and their research got also less attention (Kelsall *et al.,* 2013). However, rare diseases like common ones can cause mild, severe or very severe symptoms impairing the quality of the patients' life significantly and causing difficulties in socialization and stigmatization (Kelsall *et al.,* 2013).

In opposite with common diseases, which usually show multifactorial etiology including environmental, life style and genetic factors in their development, rare diseases are usually monogenic ones. Therefore the development of rare diseases is mostly determined by the presence or the absence of any causative genetic alteration. These specific genetic variations of a certain gene can lead to the consequential failure of the translated protein and thus to the development of the disease. According to our current knowledge, the number of different human monogenic disorders is estimated to be more than 10000 (Kelsall *et al.,* 2013; Orphanet Database; www.orpha.net). According to the data of the WHO, the global prevalence of monogenic diseases at birth is approximately 10:1000 (Kelsall *et al.,* 2013). These diseases usually follow the rules of Mendelian inheritance and show either autosomal or sex chromosome-linked and either dominant or recessive mode of transmission.

In this study, I have investigated four rare diseases – Christ-Siemens-Touraine syndrome, Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1 – with overlapping dental symptoms and different skin ones.

1.2. Christ-Siemens-Touraine syndrome

Christ-Siemens-Touraine syndrome (OMIM 305100) is a rare ectodermal dysplasia characterized by a triad of signs comprising sparse hair (hypotrichosis), abnormal or missing teeth (anodontia or hypodontia), and inability to sweat (anhidrosis or hypohidrosis). Christ-Siemens-Touraine syndrome has been reported throughout the world (Pinheiro *et al.,* 1979). It mainly affects males, heterozygous female carriers might show mild symptoms or are completely healthy. The prevalence is estimated between 1:100000 and 1:1000000 individuals (Fete *et al.,* 2014).

1.2.1. Clinical symptoms

Ectodermal dysplasias are classified as congenital disorders characterized by abnormal development in 2 or more ectodermal structures (hair, nails, teeth, and sweat glands) without other systemic findings.

Christ-Siemens-Touraine syndrome is featured by hypotrichosis of the scalp and/or the body hair. In addition, the scalp hair has thin shafts and is lightly pigmented. Although hair shafts can be brittle and twisted, these findings are not sufficiently sensitive to be of diagnostic benefit (Rouse *et al.,* 2004). Secondary sexual hair – beard, axillary and pubic hair – may be more normal.

Christ-Siemens-Touraine syndrome is also characterized by hypodontia: An average of nine permanent teeth develop in individuals with classic form, typically the canines and first molars (Lexner *et al.,* 2007). Teeth are often smaller than average and have an altered morphology; the anterior teeth frequently have conical crowns.

The third symptom of the triad is hypohidrosis. Historically, the term "anhidrotic" has been defined as the inability to perspire; "hypohidrotic" suggests impairment in the ability to perspire. Since most individuals with Christ-Siemens-Touraine syndrome have at least a limited ability to perspire, the term "hypohidrotic" more accurately reflects the condition.

1.2.2. Genetic background

The majority of individuals with hypohidrotic ectodermal dysplasia show the X-linked form. Ectodysplasin A (*EDA1*; GenBank accession number NM_001399.4) is the only gene, in which pathogenic variants are known to cause X-linked hypohidrotic ectodermal dysplasia. Pathogenic variants in *EDAR, EDARADD* and *WNT10A* genes are known to be associated with both autosomal dominant and autosomal recessive forms of hypohidrotic ectodermal dysplasia (Cluzeau *et al.,* 2011).

The *EDA1* gene comprises 12 exons and encodes a transmembrane protein, which has 391 amino acid residues and a short collagenous domain (Gly-X-Y). Ectodysplasin-A is a trimeric type II protein that colocalizes with cytoskeletal structures at the lateral and apical surfaces of cells, suggesting that it is a novel member of the tumor necrosis factor (TNF)-related ligand family that plays a role in early epithelial-mesenchyme interactions (Ezer *et al.,* 1999).

1.3. Papillon-Lefèvre syndrome

Papillon-Lefèvre syndrome (OMIM 245000) is a rare ectodermal dysplasia characterized by early-onset periodontitis associated with palmoplantar keratoderma. Papillon-Lefèvre syndrome has been reported throughout the world in a diverse range of ethnic groups and parental consanguinity has been noted in more than 50% of the cases (Gorlin *et al.,* 1964). The male to female ratio is 1:1. The prevalence is estimated between 1:250000 and 1:1000000 individuals and more than 300 cases have been reported worldwide (Gorlin *et al.,* 1964; Haneke *et al.,* 1979).

1.3.1. Clinical symptoms

Papillon-Lefèvre syndrome was first described by Paul-Henri Papillon and Paul Lefèvre in 1924 (Papillon and Lefèvre, 1924). The main characteristic features of Papillon-Lefèvre syndrome are periodontal inflammation, causing loss of both the primary and permanent teeth and symmetrical palmoplantar hyperkeratosis.

Periodontitis and gingivitis result in the loss of primary and permanent teeth (Gorlin *et al.*, 1964; Toomes *et al.*, 1999; Hewitt *et al.*, 2004; Figure 1.).

Figure 1. *Clinical pictures of the teeth loss of a patient with Papillon-Lefèvre syndrome. (a) anterior view, (b) right posterior view, (c) left posterior view (Bhavsar et al., 2013).*

Since symptoms appear as the teeth erupt, patients with Papillon-Lefèvre syndrome typically report two episodes of gingivitis: the first one at approximately 3 years of age, leading to the loss of primary teeth (Lundgren *et al.*, 2004), the second one at approximately 15 years of age, resulting in the loss of permanent teeth (Fardal *et al.*, 1998; Figure 2.).

Figure 2. *Orthopantogram of a patient with Papillon-Lefèvre syndrome (Bhavsar et al., 2013).*

Keratoderma in Papillon-Lefèvre syndrome can present in the first three months of life, although palmoplantar hyperkeratosis generally first appears in years 1–4 (Haneke *et al.*, 1979). However, several late-onset variants of Papillon-Lefèvre syndrome have also been reported (Bullon *et al.*, 1993; Pilger *et al.*, 2003). Skin symptoms include transgrediens spread with hyperkeratosis of palms and soles. Diffuse

hyperkeratosis is the most commonly observed type; however, the punctuate type occurs rarely. Generally, hyperkeratosis in Papillon-Lefèvre syndrome is not severe (Toomes *et al.*, 1999; Figure 3.). Psoriasiform lesions may also develop on the elbows, knees and knuckles (Toomes *et al.*, 1999). Since skin lesions in Papillon-Lefèvre syndrome are similar to Mal de Meleda (OMIM 248300) lesions, another rare form of palmoplantar keratodermas, Papillon-Lefèvre syndrome was first considered as a variant of Mal de Meleda. Subsequently, it was determined that the two diseases are different forms of palmoplantar keratodermas (Gorlin *et al.*, 1964).

In addition to these symptoms, recurrent skin infections and liver abscesses are frequently reported (Pham *et al.*, 2004; de Haar *et al.*, 2004; Romero-Quintana *et al.*, 2013). Moreover mild mental retardation, intracranial calcifications and hyperhidrosis can also occur (Haneke *et al.*, 1979). Japanese patients might have an increased risk of developing melanomas at the sites of hyperkeratosis (Nakajima *et al.*, 2008) than other ethnic groups.

Figure 3. *Skin symptoms of a patient with Papillon-Lefèvre syndrome (a,b) palmar keratoderma (c,d) plantar keratoderma (Khan et al., 2012).*

1.3.2. Genetic background

Papillon-Lefèvre syndrome is transmitted as an autosomal recessive condition affecting males and females equally. Papillon-Lefèvre syndrome was independently

mapped to chromosome 11q14-21 by three groups (Laass *et al.*, 1997; Fischer *et al.*, 1997; Hart *et al.*, 1998; Figure 4.). In the mapped region, the causative cathepsin C gene was independently identified by two groups (Hart *et al.*, 1999; Toomes *et al.* 1999). The cathepsin C gene (*CTSC*, GenBank accession number NM_001814.4) spans over 46 kb and contains 7 exons and 6 introns (Toomes *et al.*, 1999). According to the Ensemble genome browser (http://www.ensembl.org), this gene has nine splice variants. Of these, five occur in protein coding regions; the remaining four are non-coding transcripts.

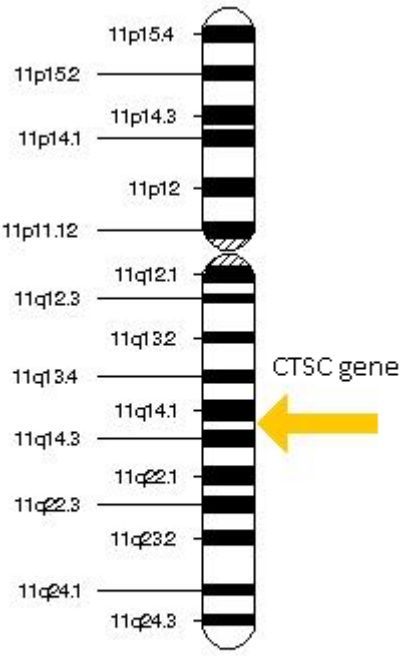

Figure 4. *Location of the CTSC gene on chromosome 11 (www.ncbi.nlm.nih.gov/gene/1075).*

CTSC encodes the cathepsin C protein (dipeptidyl-peptidase I), a lysosomalexo-cysteine proteinase belonging to the peptidase C1 family. Cathepsin C is an oligomeric enzyme composed of four identical subunits (Paris *et al.*, 1995; Dolenc *et al.*, 1995). Each subunit contains three different polypeptides — heavy, light and propeptide chains — which are held together by non-covalent interactions (Cigic *et al.*, 1998). The C-terminus of the propeptide is cleaved upon activation. The residual propeptide is cleaved into two peptides, which are held together by a disulphide bond (Cigic *et al.*, 1998).

Cathepsin C has the ability to remove dipeptides from the amino terminus of proteins and is involved in the zymogen activation of serine proteases. This activity was proposed to play a role in epithelial differentiation and desquamation (Toomes *et al.*, 1999).

1.4. Haim-Munk syndrome

Haim-Munk syndrome (OMIM 245010) is a rare ectodermal dysplasia characterized by early-onset severe periodontitis associated with palmoplantar

keratoderma, onychogryposis, pes planus, arachnodactyly and acroosteolysis (Haim and Munk, 1965). The majority of reported cases are descendants of a few consanguineous families from a religious isolate in Cochin, India (Haim and Munk, 1965; Smith and Rosenzeig, 1967; Puliyel and Sridharan Iyer, 1986). One unrelated Brazilian patient has also been reported (Cury *et al.*, 2005). The male to female ratio is 1:1. The prevalence is estimated to be 1:1000000 individuals. Haim-Munk syndrome is very rare with less than 100 cases reported in the literature so far (Haim and Munk, 1965; Smith and Rosenzeig, 1967; Puliyel and Sridharan Iyer, 1986; Cury *et al.*, 2005).

1.4.1. Clinical symptoms

Haim-Munk syndrome was first described among members of a small community of Jews from Cochin, India by Haim and Munk (1965). The main characteristic features of Haim-Munk syndrome are periodontitis associated with palmoplantar keratosis, pes planus, onychogryphosis, arachnodactyly and acroosteolysis.

The periodontium in Haim-Munk syndrome may be less severely affected than in Papillon-Lefèvre syndrome, but gingival inflammation and alveolar-bone destruction are present and severe (Janjua *et al.*, 2004; Figure 5.).

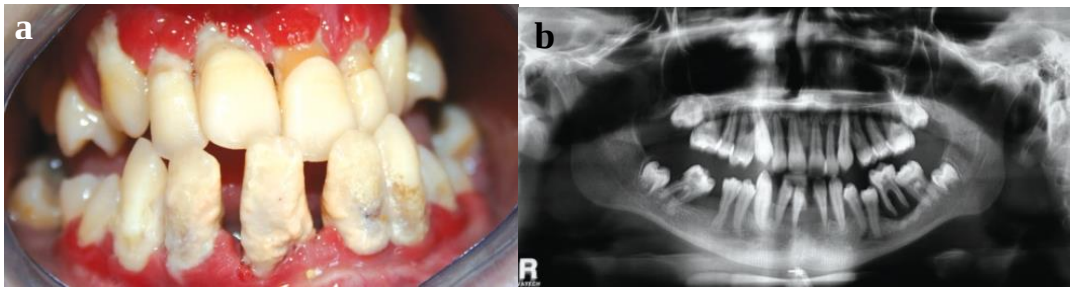

Figure 5. *Dental symptoms of a patient with Haim-Munk syndrome. (a) The gingiva around the teeth is bright red, severely inflamed, swollen, with pus exuding from the periodontal pockets and gingival abscesses. (b) The panoramic radiographs shows severe vertical and horizontal alveolar bone loss around all remaining teeth (Erciyas et al., 2010).*

In contrast to Papillon-Lefèvre syndrome, the cutaneous findings in Haim-Munk syndrome are more severe and extensive (Hartc *et al.,* 2000). Besides palmoplantar hyperkeratosis, there are several additional features including recurrent pyogenic skin infections, acroatrophic changes of nails, arachnodactyly, a peculiar radiographic deformity of the finger contapered, pointed phalangeal ends, and pes planus (Janjua *et al.*, 2008; Figure 6.).

Figure 6. *Arachnodactyly and acroosteolysis detected in patient with Haim-Munk syndrome (Erciyas et al., 2010).*

1.4.2. Genetic background

Haim-Munk syndrome is transmitted as an autosomal recessive condition affecting males and females equally. Similarly to Papillon-Lefèvre syndrome, Haim-Munk syndrome is also caused by mutations of the *CTSC* gene (Hartc *et al.,* 2000).

1.5. Aggressive periodontitis type 1

Aggressive periodontitis type 1 (OMIM 170650) is a rare ectodermal dysplasia characterized by severe periodontal inflammation leading to tooth loss (Hart *et al.,* 2000c; Hewitt *et al.,* 2004). Since other organs are not affected, aggressive periodontitis type 1 also belongs to the family of non-syndromic aggressive periodontitis. There are only a few cases in the literature, which are genetically confirmed and diagnosed as aggressive periodontitis type 1 (Hart *et al.,* 2000c; Hewitt *et al.,* 2004). Regarding these patients, the male to female ratio is 1:1. The prevalence is estimated to be less than 1:1000000 individuals (Hart *et al.,* 2000c; Hewitt *et al.,* 2004).

1.5.1. Clinical symptoms

Aggressive periodontitis, which may be generalized or localized, is characterized by severe and protracted gingival infections, leading to tooth loss. Amounts of microbial deposits are generally inconsistent with the severity of periodontal tissue destruction and the progression of attachment and bone loss may be self-arresting (American Academy of Periodontology, 2000). The term "aggressive periodontitis" replaced the terms "early-onset," "prepubertal," or "juvenile periodontitis" at a 1999 International workshop for a classification of periodontal disease and conditions, where it was decided that the classification terminology should not be age dependent or require knowledge of rates of progression (Armitage, 1999).

Aggressive periodontitis type 1 is usually characterized by dental symptoms only and other organs are not affected. The main feature of aggressive periodontitis type 1 is the severe periodontal inflammation leading to tooth loss (Hart *et al.,* 2000c; Hewitt *et al.*, 2004; Figure 7.).

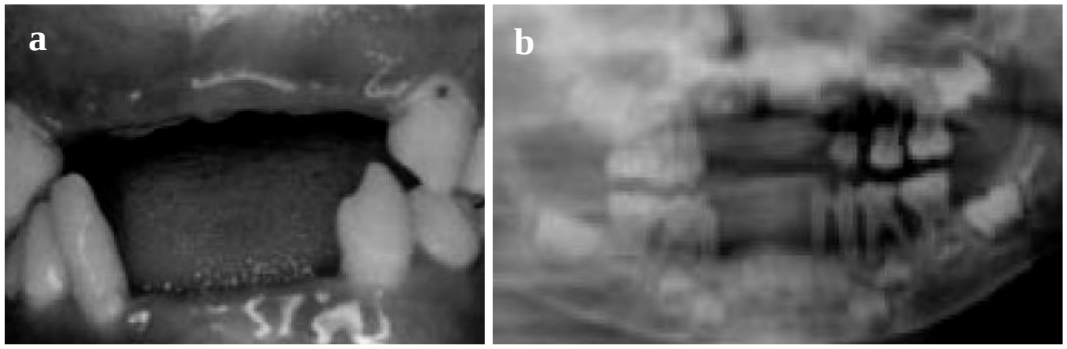

Figure 7. *Patient with aggressive periodontitis type 1. (a) Clinical and (b) X-ray pictures demonstrate gingival recession and advanced alveolar bone loss around remaining primary dentation (Hart et al., 2000c).*

1.5.2. Genetic background

Aggressive periodontitis type 1 is transmitted as an autosomal recessive condition affecting males and females equally. Similarly to Papillon-Lefèvre and Haim-

Munk syndromes, aggressive periodontitis type 1 is also caused by mutations of the *CTSC* gene (Hart *et al.,* 2000c).

1.6. Same cause, same disease

Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1 have some overlapping and some distinctive clinical features, therefore earlier they were considered as different entities. In 1999, with the identification of their causative gene, the *CTSC* gene, their common genetic background was identified (Hart *et al.,* 1999; Toomes *et al.,* 1999). First it was suggested that different mutations of the *CTSC* gene might lead to the development of different disease, but genotyping patients with Papillon-Lefèvre syndrome, Haim-Munk syndrome or aggressive periodontitis type 1 did not confirm this hypothesis.

To date, a total of 75 mutations have been reported for the *CTSC* gene. The majority of the mutations (97%) were reported in patients with Papillon-Lefèvre syndrome, while only a few mutations (3%) were reported in patients with either Haim-Munk syndrome or aggressive periodontitis type 1.

To note, some mutations of the *CTSC* gene were detected in two different disease entities: The c.1040A>G p.Tyr347Cys missense mutation was reported in patients with aggressive periodontitis type 1 and also in patients with classic Papillon-Lefèvre syndrome (Toomes *et al.,* 1999; Hart *et al.,* 2000c; Hewitt *et al.,* 2004). The c.145C>T p.Gln49X nonsense mutation was reported for Haim-Munk syndrome and for Papillon-Lefèvre syndrome pedigrees (Selvaraju *et al.,* 2003; Rai *et al.,* 2010). The c.857A>G p.Gln286Arg missense mutation was present in patients with the phenotype of either Haim-Munk syndrome or Papillon-Lefèvre syndrome (Hart *et al.,* 2000b). These genetic findings suggest, that Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1 are not different entities, but they represent the phenotypic spectrum of a single disease (Table I.). Therefore in the followings, the diagnosis of Papillon-Lefèvre syndrome is used in this study.

	Papillon-Lefèvre syndrome	**Haim-Munk syndrome**	**Aggressive periodontitis type 1**
OMIM ID	245000	245010	170650
Clinical symptoms			
Periodontitis	✓	✓	✓
Palmoplantar keratoderma	✓	✓	✗
Pes planus	✗	✓	✗
Onychogryphosis	✗	✓	✗
Arachnodactyly	✗	✓	✗
Acroosteolysis	✗	✓	✗
Genetic background			
CTSC mutations	✓	✓	✓

Table I. *Comparison of the clinical features and genetic background of Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1.*

1.7 Aims

In this study, I have investigated the Christ-Siemens-Touraine syndrome and the allelic variants of Papillon-Lefèvre syndrome, which include Haim-Munk syndrome and aggressive periodontitis type 1. These variants show overlapping dental symptoms and different other ones.

I aimed to investigate Hungarian pedigrees and sporadic cases with Papillon-Lefèvre syndrome. After performing the relevant, adequate dental care for these patients,

I have initiated dermatological investigations to perform complete workup for these patients.

Besides the teamwork of the clinical care, I have also initiated genetic screening for these patients to help them in family planning and also to elucidate the genotype-phenotype correlations of the disease. Therefore I aimed to compare the clinical symptoms and the identified mutations in all investigated patients. After comparing Hungarian patients to each other, I have also compared their data with the so far reported ones in the literature. To do this, I have performed literature search (http://www.ncbi.nlm.nih.gov/pubmed) to identify the reported patients Papillon-Lefèvre syndrome and all the known *CTSC* mutations.

2. Patients and methods

2.1. Patients

However Christ-Siemens-Touraine and Papillon-Lefèvre syndrome are rare diseases, there are several patients under my dental care. In this study, I will describe three families and two sporadic cases in details, in whom the genetic investigations identified the causative abnormalities.

In Hungary, mutation screening for the *EDA1* and *CTSC* genes have been available since 2011. Screening is performed with direct sequencing of all coding regions and flanking introns of the *EDA1* and *CTSC* genes. Once a putative causative variant was identified in a patient, the available, clinically symptom-free family members and unrelated, healthy control individuals were also investigated.

2.1.1. Pedigree I

I have recently identified a 35-year-old Hungarian patient with Christ-Siemens-Touraine syndrome and with characteristic dysmorphic facial features, sparse hair, reduced sweating and missing teeth (Figure 8.).

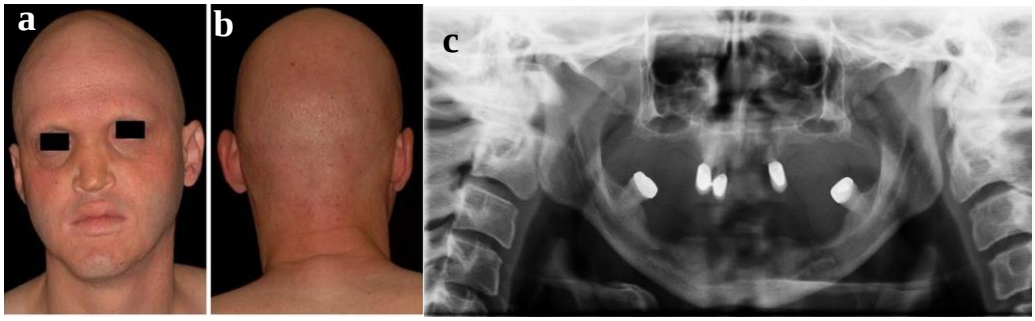

Figure 8. *Clinical symptoms of the patient with Christ-Siemens-Touraine syndrome: (a) missing eyebrows and eyelashes, (b) sparse hair and (c) hypodontia (Kinyo et al., 2014).*

On investigation the classic triad of Christ-Siemens-Touraine syndrome was present. Dermatological symptoms included sparse hair and reduced sweating and dental symptoms highlighted hypodontia.

The investigated patient (II/3) is the only affected family member who exhibits the complete triad with sparse hair, missing teeth and reduced sweating. His sister (II/2) and his daughter (III/1) also have some conical-shaped teeth, but otherwise they are healthy. The older brother of the patient (II/1) died at the age of 4 months due to hyperpyrexia. The symptomless parents reported on a 16-year-old sister of the affected daughters, who has no symptoms as well as the parents (Kinyo *et al.*, 2014; Figure 9.).

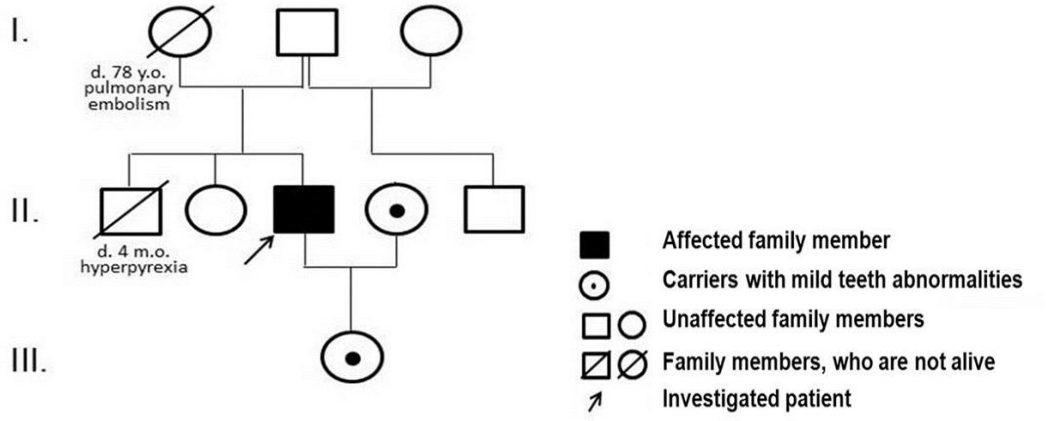

Figure 9. *Pedigree of the investigated family spreading three generations and containing one affected individual (Kinyo et al., 2014).*

2.1.2. Pedigree II

I have recently identified a Hungarian family with two sisters affected with severe periodontitis leading to the loss of all primary teeth (Figure 10.).

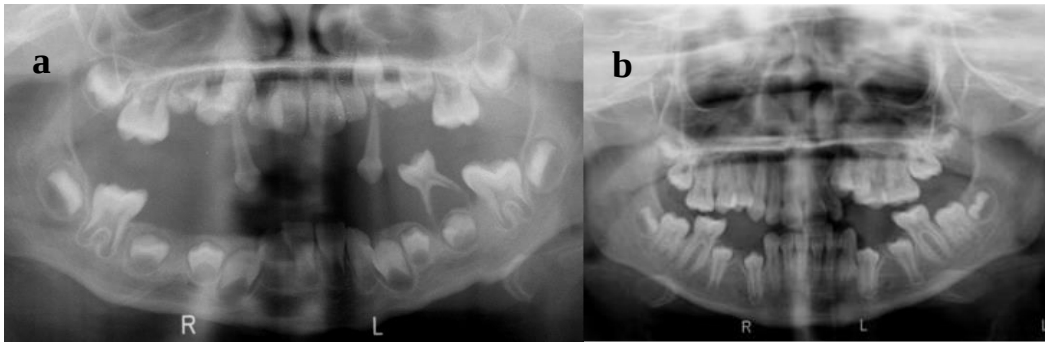

Figure 10. *X-ray pictures show the dental symptoms of the older one (Patient I) of the siblings affected by Papillon-Lefèvre syndrome. (a) The first picture was taken in 2006, (b) the second one in 2011.*

On dermatological investigation an 11-year-old Hungarian girl (Patient I) was referred with the typical skin symptoms of Papillon-Lefèvre syndrome, complicated with palmoplantar eruption. On referral sharply circumscribed erythema with minimal hyperkeratosis and shedding was seen on both palms (Farkas *et al.*, 2013; Figure 11).

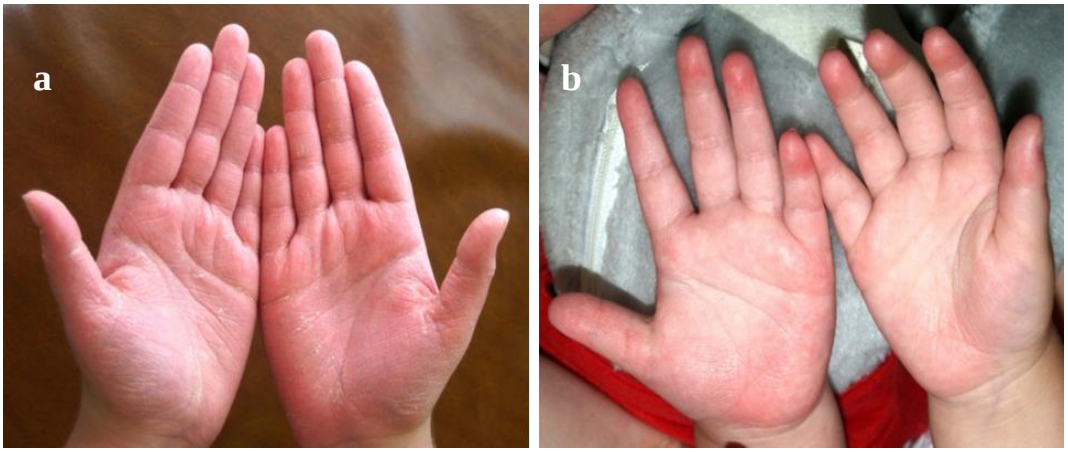

Figure 11. *Palmar skin symptoms of the two investigated siblings affected by Papillon-Lefèvre syndrome: (a) Patient I, (b) Patient II (Farkas et al., 2013).*

The erythema on the plantar surfaces was minimal, however hyperkeratosis with deep fissures dominated (Farkas *et al.*, 2013; Figure 12). These abnormalities first appeared at her age of 19 months (Farkas *et al.*, 2013).

Figure 12. *Plantar skin symptoms of the two investigated siblings affected by Papillon-Lefèvre syndrome: (a) Patient I, (b) Patient II (Farkas et al., 2013).*

The other patient (Patient II) was a 2-year-old Hungarian girl, the younger sister of Patient I. She was also referred with having similar symptoms as her older sibling. Palmoplantar eruptions started at her age of 10 months. On referral, minimal erythema was seen on the distal fingertips (Farkas *et al.*, 2013; Figure 9.) and erythema with minimal hyperkeratosis was present on the soles of the feet (Farkas *et al.*, 2013; Figure 10.).

The symptomless parents reported on a 16-year-old sister of the affected daughters, who has no symptoms as well as the parents (Farkas *et al.*, 2013; Figure 13.).

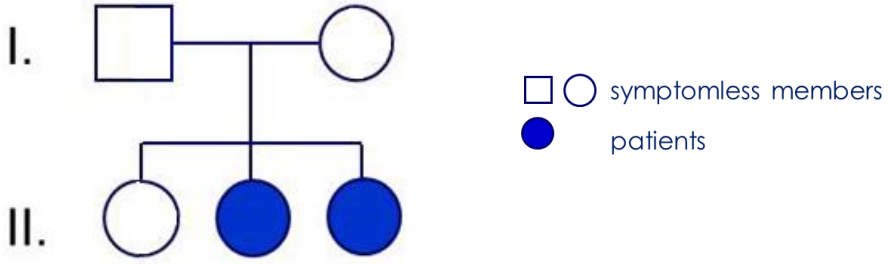

Figure 13. *Pedigree of the investigated family spreading two generations and containing two affected siblings (Farkas et al., 2013).*

2.1.3. Pedigree III

There is another pair of affected siblings, who are also under my regular dental care. In this Hungarian family the affected two sisters were referred to our out-patient dental clinic years ago with severe tooth loss due to severe periodontitis (Figure 14.).

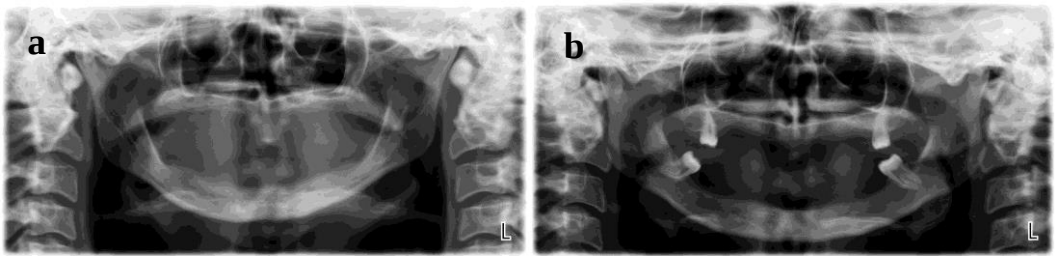

Figure 14. *Orthopantograms show dental symptoms of the affected siblings, (a) Patient I, (b) Patient II.*

Regarding their dermatological symptoms, there is a significant contrast between the severity of the palmar and the plantar hyperkeratosis. The sisters show very mild palmar symptoms on both hands, it looks like hand dryness (Figure 15.).

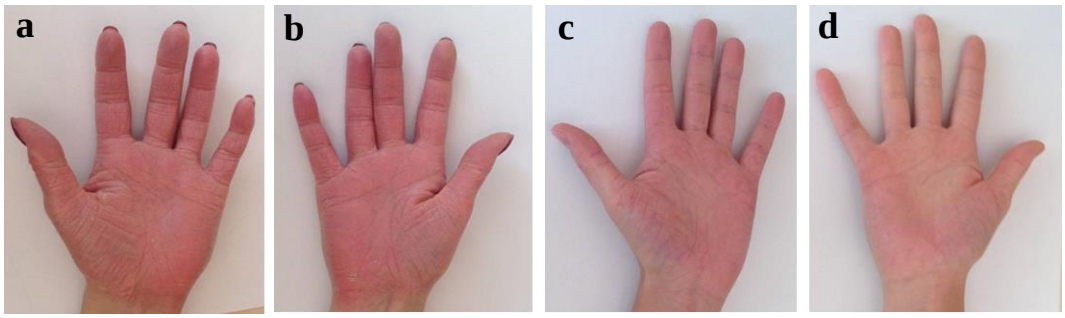

Figure 15. *Palmar skin symptoms of the two investigated siblings affected by Papillon-Lefèvre syndrome: (a) left and (b) right hand of Patient I, (c) left and (d) right hand of Patient II.*

In opposite with their hands, the hyperkeratosis on their soles is very severe (Figure 16.).

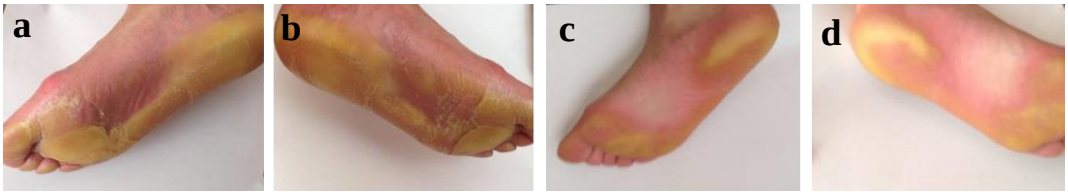

Figure 16. *Plantar skin symptoms of the two investigated siblings affected by Papillon-Lefèvre syndrome: (a) right and (b) left feet of Patient I, (c) right and (d) left feet of Patient II.*

The symptomless parents reported on having no other affected or symptomless child. Since these siblings are now young adults, Patient I is 24 and Patient II is 28-yeard-old. I have performed dental investigations and complete clinical and genetic workup for their symptomless partners as well (Figure 17.).

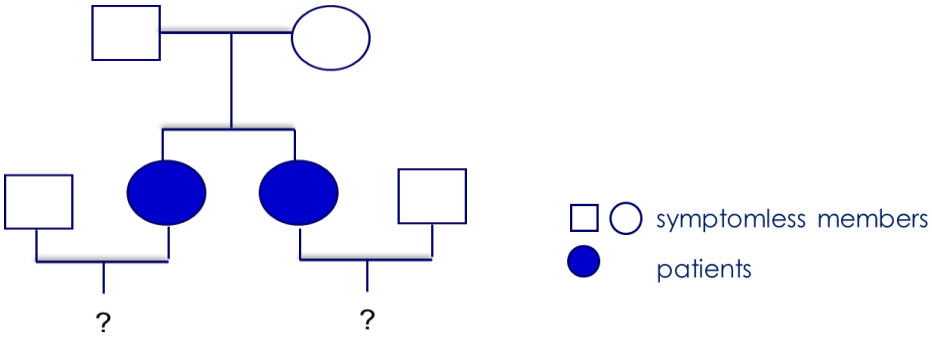

Figure 17. *Pedigree of the investigated family spreading two generations and containing two affected siblings.*

2.1.4. Sporadic case I

A 39-year-old Hungarian woman was referred from the Mór Kaposi Teaching Hospital (Kaposvár) with a common phenotype of Papillon-Lefèvre syndrome. The patient was presented with the typical skin symptoms of Papillon-Lefèvre syndrome. She has lost all her permanent teeth and has permanent prosthesis. Hyperkeratotic plaques were seen on both palms and soles (Figure 18). Besides these symptoms, arachnodactily was also present on the right hand raising the possibility of the allelic variant of the Papillon-Lefèvre syndrome, the Haim-Munk syndrome (Figure 18).

Figure 18. *Clinical symptoms of the patient affected by Haim-Munk syndrome, the allelic variant of Papillon-Lefèvre syndrome: (a) mild palmar hyperkeratosis, (b) arachnodactily and (c) moderate hyperkeratosis of the palms.*

2.1.5. Sporadic case II

A 25-year-old Hungarian man unrelated to the previous 39-year-old Hungarian woman. He was also referred from the Mór Kaposi Teaching Hospital (Kaposvár) with complete teeth loss and hyperkeratotic skin symptoms on his palms and soles. He does not show arachnodactily (Figure 19.).

Figure 19. *Clinical symptoms of the patient affected by Papillon-Lefèvre syndrome: (a) mild palmar hyperkeratosis, (b) no sign of arachnodactily and (c) moderate hyperkeratosis of the palms.*

2.2. Methods

All patients are in complete clinical care including dental and dermatological care. Written informed consents were obtained from all investigated individuals during pre-test genetic counselling before genetic investigations were carried out. The investigated individuals were informed about the results of the investigations during post-test genetic counselling. The study was conducted according to the Principles of the Declaration of Helsinki.

2.2.1. DNA isolation

Blood samples were taken from the patients and from the clinically unaffected family members (Figure 20.). Genomic DNA was isolated from whole blood samples using a QIAamp DNA Blood Mini Kit (QIAGEN; Hilden, Germany). During the isolation, after proteinase K digestion, washings with alcohol were done following the instructions. Genomic DNA was dissolved in 100 µl distilled water.

2.2.2. Polymerase chain reaction

During polymerase chain reaction (PCR) amplification (Figure 20.), 4 µl genomic DNA was used as template. In addition, the reaction mix contains 9 µl Dream Taq Green PCR Master Mix (Fermentas), 4 µl distilled water, 1.5 µl forward and 1.5 µl reverse primers. The using primers sequences obtained from the UCSC Genome Browser and Primer3 and listed in Table II.

During PCR reaction, the 2^{nd}, 3^{rd} and 4^{th} steps were repeated 40 times. The annealing temperature and the number of the cycles were depended on the primers, the synthesis reaction time was determined according to the length of the reaction product.

PCR reaction was carried out with the conditions listed in Table III.

Primer	5'-3' sequence
CTSC-X1-F	CTCGGCTTCCTGGTAATTCTT
CTSC-X1-R	GAAGCGGTAGTTGGCGTG
CTSC-X2-F	CAAACTGGGTAGCATGAAAGG
CTSC-X2-R	GAGTGGTGTCAATTCCGGTC
CTSC-X3-F	GCCATGGAAATGGACCTG
CTSC-X3-R	TGGTCCATTACTTTTGGAACACT
CTSC-X4-F	GCACAGAGTGTGAATGCCTG
CTSC-X4-R	AGGACTGCTTAGGAGGGAGG
CTSC-X5-F	GGAAATCATCCTCAAAGGAAAG
CTSC-X5-R	GTATCCCCGAAATCCATCAC
CTSC-X6-F	TGCATGATTCTCTGTGAGGC
CTSC-X6-R	GGCCAGACTTGCACTCAGAT
CTSC-X7a-F	TTCAGGGGTAACATGCAAAG
CTSC-X7a-R	CATAGCCCACAAGCAGAACA
CTSC-X7b-F	CTGCAATGAAGCCCTGATG
CTSC-X7b-R	GATTGCTGCTGAAAGTCTACAGTC

Table II. *The list of primers used for the genetic investigations.*

Step	Temperature (°C)	Time (sec)	Process
I.	95	600	
II.	95	30	denaturation
III.	59	30	annealing
IV.	72	45	synthesis
V.	72	600	
VI.	4	∞	

Table III. *Conditions of the PCR reactions.*

2.2.3. Gel electrophoresis

The PCR products were checked on 2% agarose gel (SeaKem LE agaróz, Lonza) using TBE buffer (Lonza) and visualized by 2.5 µl GelRed (Biotium) staining (Figure 18.). The gel was analyzed by BioRad Molecular Imager® GelDoc™ XR gel documentation system with QuantityOne software.

2.2.4. Sequencing

The sequencing was performed after the suitable purifying of the PCR reaction products using Big Dye Terminator v3.1 Cycle sequencing kit (Applied Biosystems) with ABI Prism 7000 (Applied Biosystems) sequencing machine (Figure 18.). The service of the sequencing was offered by Delta Bio 2000 Kft.

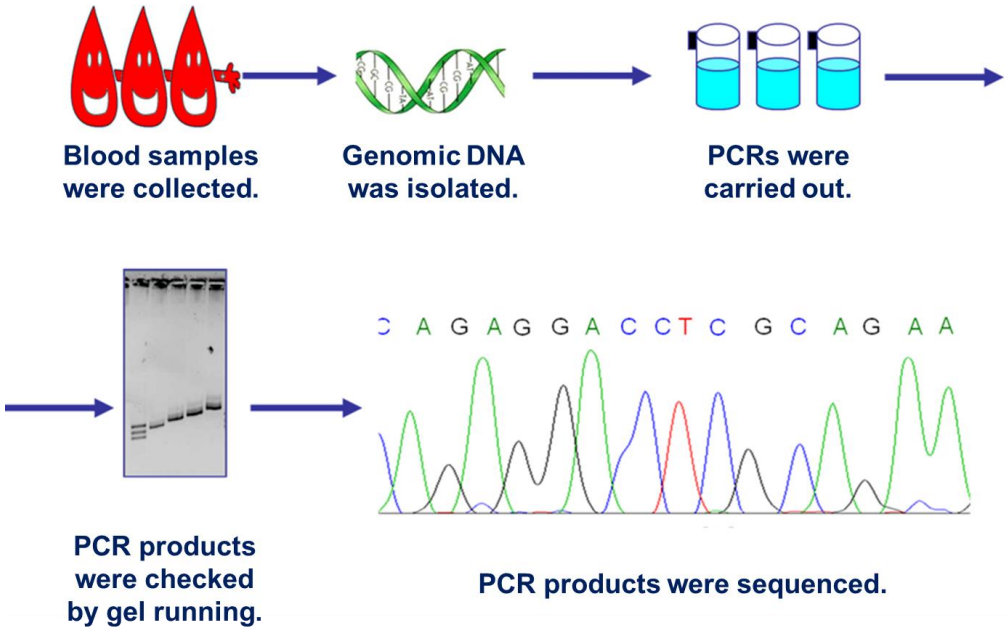

Figure 20. *Summary of the applied genetic investigations. Blood samples were taken from all investigated individuals, then DNA was isolated. Using specific primers PCR reactions were carried out. The PCR products were checked on agarose (1.5%) gel electrophoresis and then they were sequenced.*

3. Results

3.1. Patient in Pedigree I carried hemizygous missense mutation

Direct sequencing of the coding regions and the flanking introns of the *EDA1* gene revealed a novel missense mutation in the eight exon (c.971T/A, p.Val324Glu; Figure 21.). The investigated healthy controls carried only wild-type sequences.

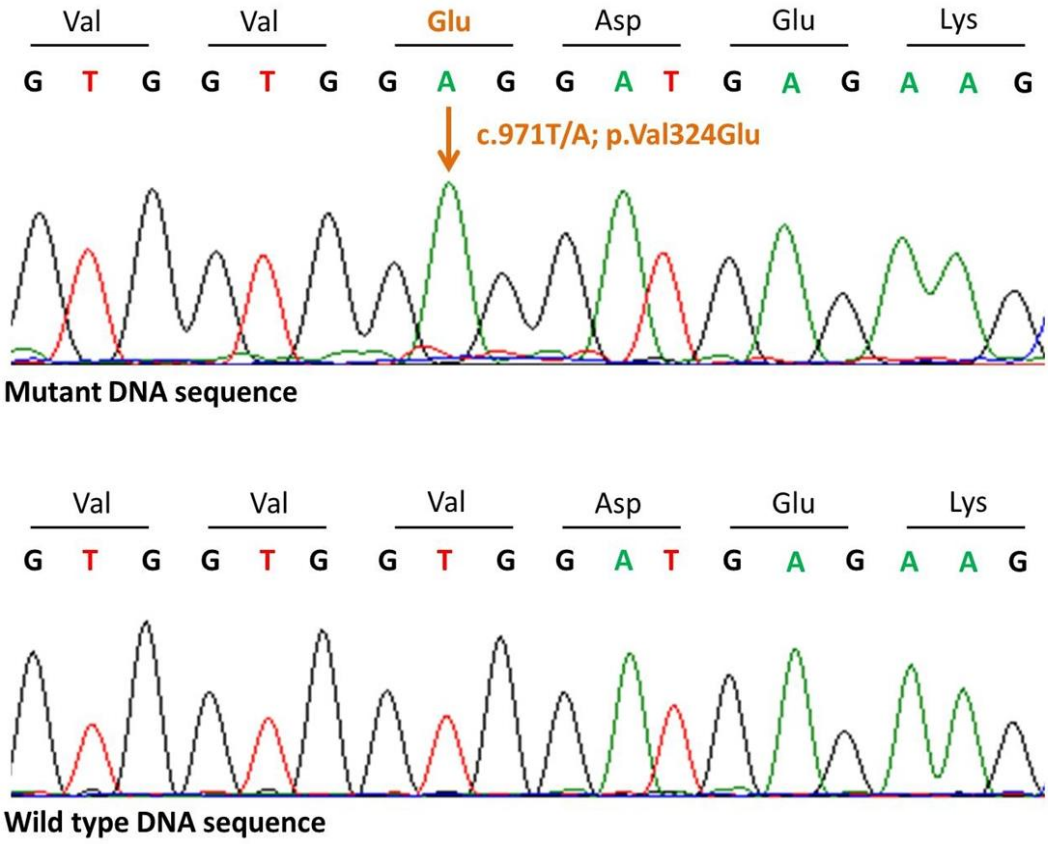

Figure 21. *The identified hemizygous missense mutation in the patient with Christ-Siemens-Touraine syndrome (Kinyo et al., 2014).*

The identified p.Val324Glu missense mutation is located in the TNF domain of the ectodysplasin protein. Therefore this genetic variant may affect the ectodysplasin/NFκB signaling pathway.

3.2. Patients in Pedigree II carried homozygous deletion

Direct sequencing of the coding regions and the flanking introns of the *CTSC* gene revealed a seven-base deletion in the fourth exon (c.566delCATACAT, p.T189fsX199; Figure 22.). This deletion causes frameshift and leads to the development of a premature termination codon (TGA) 32 bases downstream of the mutation.

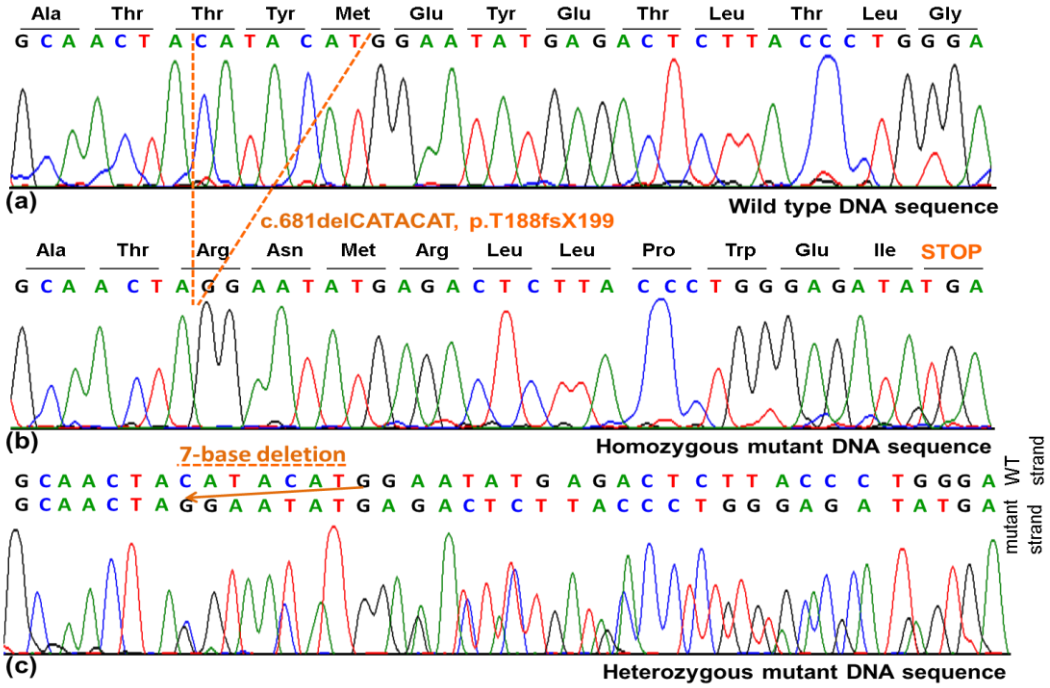

Figure 22. *The identified homozygous seven-base deletion in the patients of Pedigree II.*

The patients carried the mutation in homozygous form (Farkas *et al.*, 2013; Figure 23.), while the unaffected family members – the parents and the symptomfree sister – carried the same mutation in heterozygous form (Farkas *et al.*, 2013; Figure 23.). The unrelated controls carried the wild type sequence. The family was not aware of consanguinity.

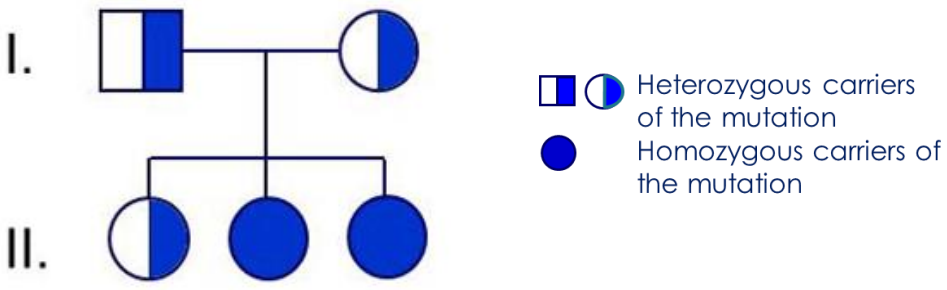

Figure 23. *Summary of the results of the genetic investigations.*

This frameshift mutation has also been previously published for two Moroccan patients with Papillon-Lefèvre syndrome (Noack *et al.*, 2008; Figure 24.).

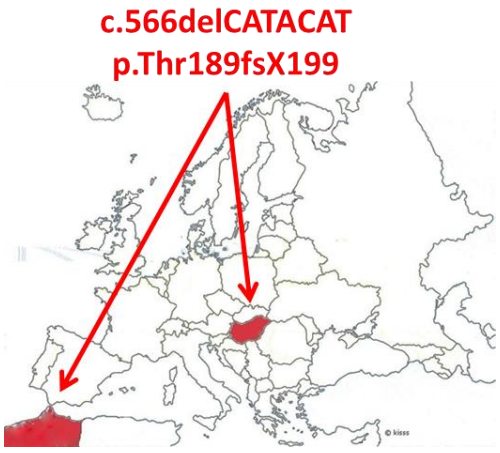

Figure 24. *The identified deletion was reported also in Moroccan patients.*

3.3. Patients in Pedigree III carried homozygous missense mutation

Direct sequencing of the coding regions and the flanking introns of the *CTSC* gene revealed a missense mutation in the seventh exon (c.901G/A, p.G301S; Figure 25.). This missense mutation causes amino acid change in the cathepsin C protein.

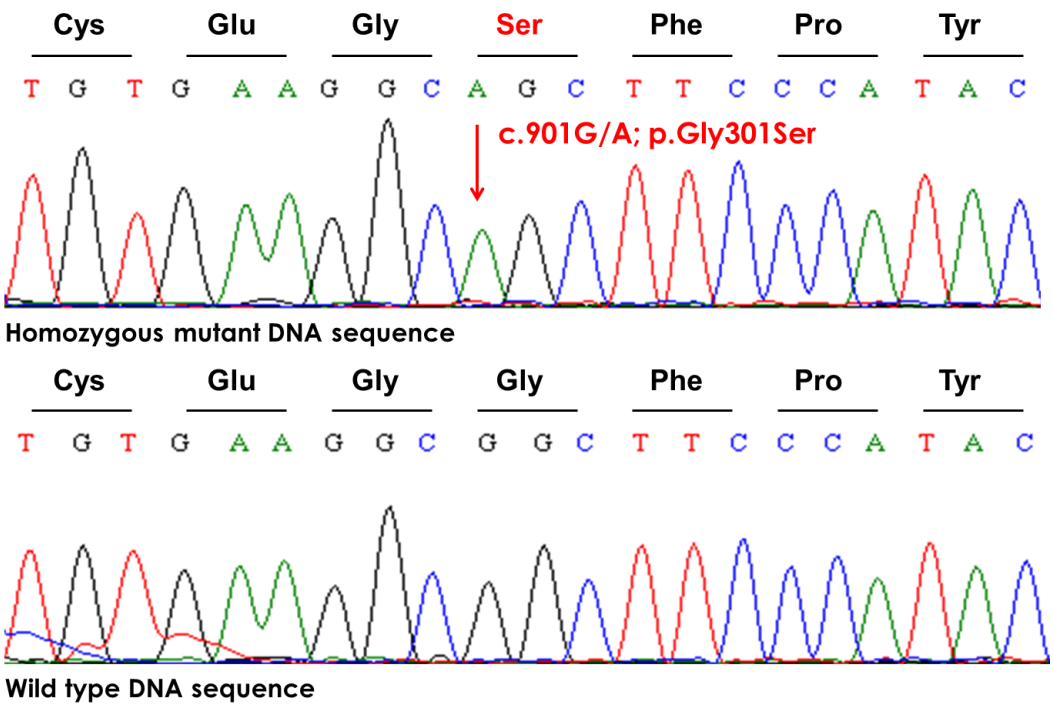

Figure 25. *The identified homozygous missense mutation in the patients of Pedigree III.*

The patients carried the mutation in homozygous form (Figure 26.), while the symptomfree partners of the patients carried the wild type sequence. The unrelated controls carried the wild type sequence as well. The family was not aware of consanguinity.

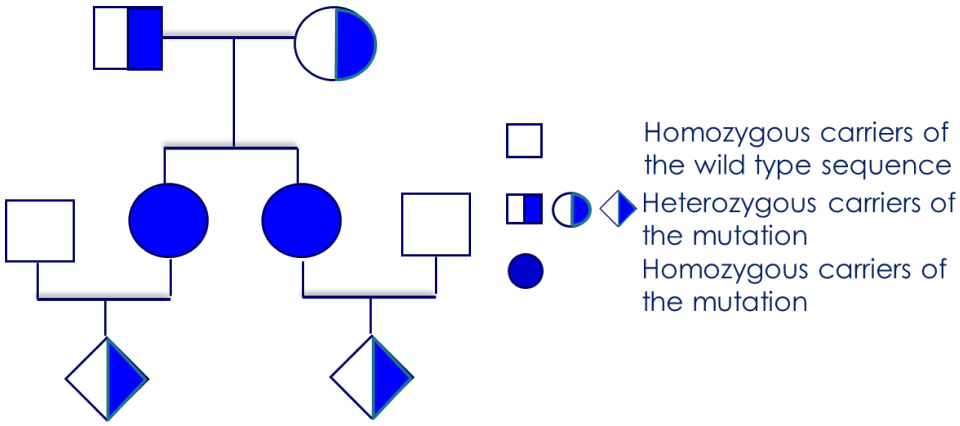

Figure 26. *Summary of the results of the genetic investigations.*

This mutation has also been previously published for a German patient with typical Papillon-Lefèvre syndrome (Noack *et al.*, 2008; Figure 27.)

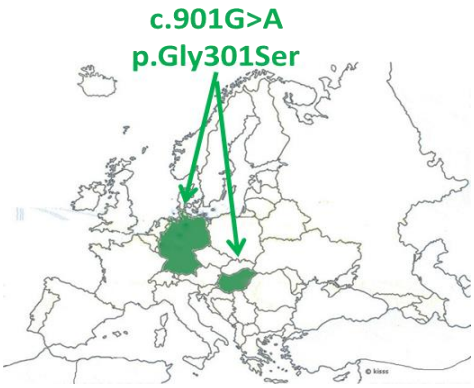

Figure 27. *The identified missense mutation was previously reported in German patients (Noack et al., 2008).*

3.4. The unrelated cases carried the same nonsense mutation

In a pair of unrelated Hungarian patients with Papillon-Lefèvre syndrome, we have identified a nonsense mutation in the fifth exon (c.748C/T, p.R250X; Figure 28.) using direct sequencing of the coding regions and the flanking introns of the *CTSC* gene. This missense mutation causes truncation of the cathepsin C protein.

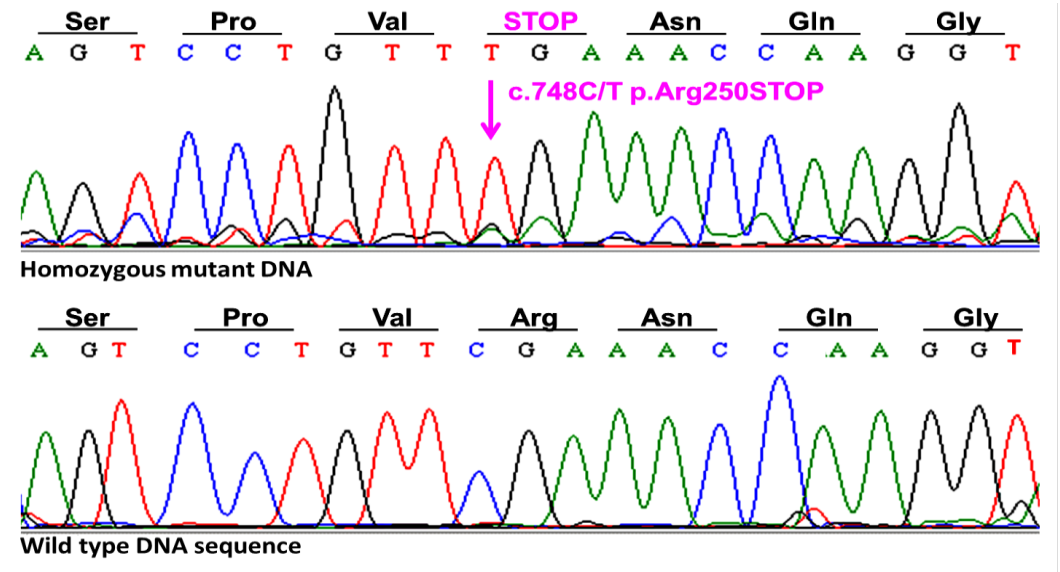

Figure 28. *The identified homozygous nonsense mutation in the unrelated patients with Papillon-Lefèvre syndrome.*

Unfortunately, both of these patients were grown up in state care and not aware of any known relatives; therefore, investigation of the family was not possible. The fact that both individuals carry the same mutation raises the possibility that these patients somehow are relatives. This mutation has also been previously published in the literature in a Turkish family with Papillon-Lefèvre syndrome (Hart *et al.*, 2000a; Figure 29.).

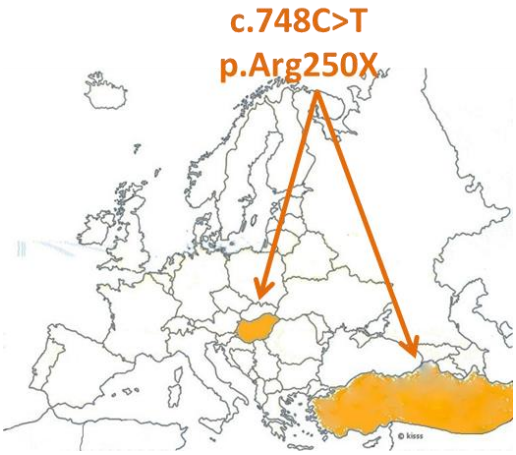

Figure 29. *The identified nonsense mutation was previously reported in Turkish patients (Hart et al., 2000a).*

4. Discussion

4.1. Significance of the investigations in the *EDA1* gene

My investigations have identified a novel hemizygous missense mutation (c.971T/A, p.Val324Glu) of the *EDA1* gene in a Hungarian patient with Christ-Siemens-Touraine syndrome.

It is interesting to note that previous studies have reported missense *EDA1* mutations in non-syndromic tooth agenesis, suggesting that dental tissues are particularly sensitive to ectodysplasin protein abnormalities (Tao *et al.*, 2006; Li *et al.*, 2008). These previous findings are in good accordance with our data, as the sister and the daughter of the investigated patient, both of whom are heterozygous carriers of the identified mutation, have some conical-shaped teeth, but exhibit otherwise normal phenotype. The investigated male patient, who is a hemizygous carrier of the mutation, shows full expression of the Christ-Siemens-Touraine phenotype with severe dental abnormalities: he developed only seven permanent, conical-shaped teeth and thus currently uses a permanent dental prosthesis.

Since the novel hemizygous missense mutation (c.971T/A, p.Val324Glu) is located in a highly conserved region within the TNF domain of the ectodysplasin protein (Figure 30.), it is hypothesized that this mutation affects the NFκB signaling pathway.

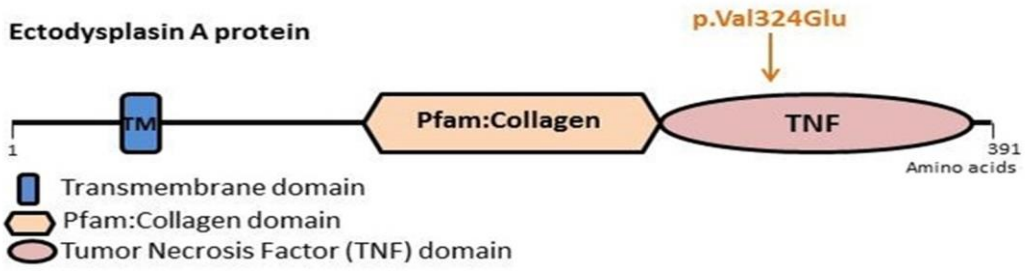

Figure 30. *The identified novel missense mutation is located in the TNF domain of the ectodysplasin A protein (Kinyo et al., 2014).*

4.2. Variants in the *CTSC* gene

To date, a total of 75 mutations have been identified for the *CTSC* gene (Figure 31.). Mutations are named according to Human Genome Variation Society (HGVS) nomenclature guidelines (www.HGVS.org) and numbered with respect to the *CTSC* gene reference sequence (ENSG00000109861 corresponding to the CTSC gene transcript ENST00000227266).

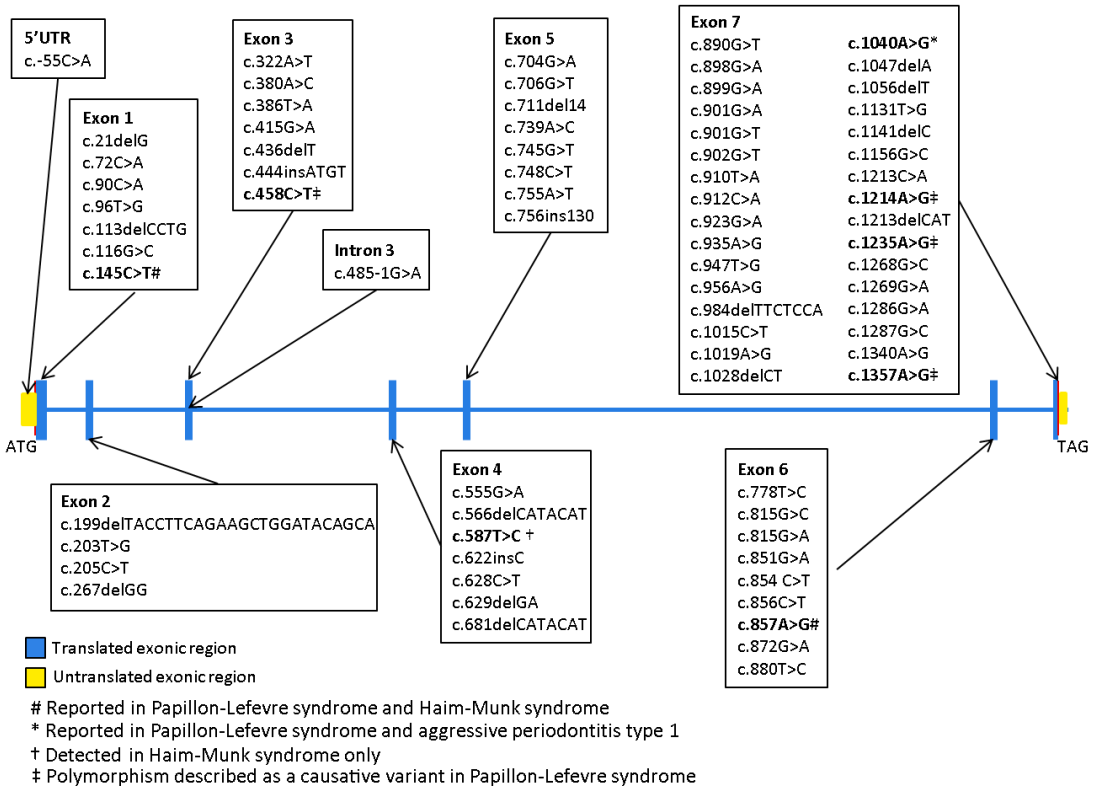

Figure 31. *Schematic drawing of the CTSC gene, indicating the positions of mutations leading to Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1. Identical mutations can lead to different diseases. The involvement of mutations in specific diseases is indicated as follows: #, Papillon-Lefèvre syndrome and Haim-Munk syndrome; *, Papillon-Lefèvre syndrome and aggressive periodontitis type 1; †, Haim-Munk syndrome; ‡, common missense variants reported as causative for Papillon-Lefèvre syndrome (Nagy et al., 2014).*

Of the reported 75 mutations, 53% are missense (n=40), 23% are nonsense (n=17) and 17% are frameshift (n=13) variants. There are two in-frame deletions, one

intronic splice-site variant and one point mutation in the 5' untranslated region of the *CTSC* gene. The majority (75%, n=56) of the mutations has only been reported once. Among these, 65% (n=36) were present in homozygous form in the investigated patients, while 35% (n=20) occurred in a compound heterozygous form. Recurrent mutations (25% of all mutations, n=19) occurred both in homozygous and in compound heterozygous forms and were detected in geographically distant, unrelated families, suggesting mutational clustering on the *CTSC* gene. However, there are also examples in the literature describing that the same initial founder effect and the subsequent migration of carriers can lead to the presence of the same mutation in geographically distant and unrelated families (Zhang *et al.,* 2001; Kurban *et al.,* 2009).

The known mutations, that have been sequenced, are unequally distributed on the *CTSC* gene. Half of the mutations (53%, n=41) are located within exons 5–7, encoding amino acids 231 to 394 in the heavy chain region. Of the remaining half, 16% (n=12) are located within exons 1–3 encoding amino acids 25 to 134 in the exclusion domain, 12% (n=9) are located within the second half of exon 7 encoding amino acids 395 to 463 in the light chain region, 13% (n=10) are located within exon 4 and the first half of exon 5 encoding amino acids 135 to 230 in the propeptide region, 3% (n=2) are located in the 5' end of exon 1 encoding amino acids 1 to 24 in the signal peptide region and 3% (n=2) are located within untranslated regions.

4.3. Ethnic variation

Papillon-Lefèvre syndrome has been reported in a diverse range of ethnic groups from all over the world. A quarter (25%, n=19) of the mutations have been reported twice or more in different ethnic groups. One of the most frequently reported missense mutation, the c.815G>Cp.Arg272Pro variant, has been detected in Lebanese, Turkish, Saudi, Holland, Russian and French patients (Toomes *et al.,* 1999, Lefevre *et al.,* 2001, Zhang *et al.,* 2002, Pham *et al.,* 2004, de Haar *et al.,* 2004, Noack *et al.,* 2008), while another frequent nonsense mutation, c.96T>Gp.Tyr32X, has been observed in patients from Mexico and France (Lefevre *et al.,* 2001, Zhang *et al.,* 2002, Pham *et al.,* 2004).

Mutation on Allele 1	Mutation type	Mutation on Allele 2	Mutation type	References
c.96T>G p.Tyr32X	nonsense	c.380A>C p.His127Pro	missense	Lefevre et al., 2001; Pham et al., 2004; Zhang et al., 2002
		c.815G>A p.Arg272His	missense	
c.322A>T p.Lys108X	nonsense	c.436delT p.Ser146fsX30	frameshift	Noack et al., 2008
		c.504C>G p.Tyr168X	nonsense	
c.415G>A p.Gly139Arg	missense	c.72C>A p.Cys24X	nonsense	Cagli et al., 2005; Hewitt et al., 2004; Yang et al., 2007
		c.706G>T p.Asp236Tyr	missense	
		c.778T>C p.Ser260Pro	missense	
		c.1141delC p.Leu381fsX13	frameshift	
c.706G>T p.Asp236Tyr	missense	c.415G>A p.Gly139Arg	missense	Allende et al., 2001; Hewitt et al., 2004
		c.872G>A p.Cys291Tyr	missense	
c.815G>C p.Arg272Pro	missense	c.96T>G p.Tyr32X	nonsense	de Haar et al., 2004; Lefevre et al., 2001; Noack et al., 2008; Pham et al., 2004;
		c.1141delC p.Leu381fsX13	frameshift	
c.1141delC p.Leu381fsX13	frameshift	c.415G>A p.Gly139Arg	missense	Lefevre et al., 2001
		c.815G>C p.Arg272Pro	missense	

Table IV. *The most frequent compound heterozygous pathogenic combinations of CTSC mutations.*

Moreover, a common frameshift mutation, c.566delCATACAT p.Thr189fsX200, has been found in Hungarian and Moroccan patients (Noack *et al.*, 2008, Farkas *et al.*, 2013). Haplotype analyses of different cases carrying identical mutations revealed that these relatively frequent mutations resulted from independent founder events. Two Turkish families carrying the same homozygous nonsense mutation (c.856C>T p.Gln286X exhibited different haplotypes, suggesting that the same mutation arose in

the two families independently (Hart *et al.*, 1998 and 2000a). The most common mutations are summarized in Table IV.

4.4. Biological relevance

Cathepsin C is a lysosomal cysteine protease that was first characterized as an activator of serine proteases from immune and inflammatory cells (Turk *et al.*, 2001). Cell lines derived from cathepsin-C-deficient mice fail to activate groups of serine proteases. Unprocessed proteases zymogens included granzymes A, B and C, cathepsin G, neutrophil elastase and chymase (Adkinson *et al.*, 2002).

The encoded cathepsin C precursor contains 463 amino acids and includes a signal peptide (24 amino acids), an exclusion domain (110 amino acids), a propeptide (96 amino acids), as well as heavy (164 amino acids) and light (69 amino acids) chain regions (Turk *et al.*, 2001; Hewitt *et al.*, 2004). Precursor cathepsin C is processed into the mature form by at least four cleavages of the polypeptide (Turk *et al.*, 2001; Adkinson *et al.*, 2002). The signal peptide is removed during translocation or secretion of the protein (Turk *et al.*, 2001; Adkinson *et al.*, 2002). The exclusion domain is retained in the mature enzyme and separated from the heavy and light chains by excision of a minor C-terminal portion of the propeptide region. The heavy and light chains are also generated by cleavage (Turk *et al.*, 2001; Adkinson *et al.*, 2002).

According to a BLAST (http://blast.ncbi.nlm.nih.gov/) search, the cathepsin C protein is highly conserved in vertebrates: the human cathepsin C shows 82% sequence similarity with the sequence from dog, 70% with turkey and 63% with frog and zebrafish. The most highly conserved regions are the heavy chain, the light chain and the C-terminal portion of the exclusion domain, which is thought to be important for enzyme activity.

Half (53%, n=40) of all *CTSC* gene mutations affect the heavy chain domain and result in different positioning of its N-terminus. Since the N-terminal region is involved in oligomer contacts with the N-terminal region of the light chain, the mutation may interfere with tetramer formation (Turk *et al.*, 2001). This finding indicates that tetramerization of the cathepsin C enzyme is crucial for its function. The majority of the

two most common types of *CTSC* mutations (missense and nonsense) affect this domain (Figure 28.).

Sixteen percent (n=12) of all *CTSC* mutations affect the exclusion domain, which blocks access to the active site and prevents substrates from binding any part except their N-termini. Thirteen mutations were detected in the exclusion domain; of these, six are nonsense variants, four are missense mutations, and three are deletions (two resulting in frameshift and one in an in-frame deletion).

Thirteen percent (n=10) of all *CTSC* gene mutations affect the propeptide fragment, which plays a pivotal role in the activation of the cathepsin C precursor. The majority of frameshift mutations are located in this domain (Figure 32.).

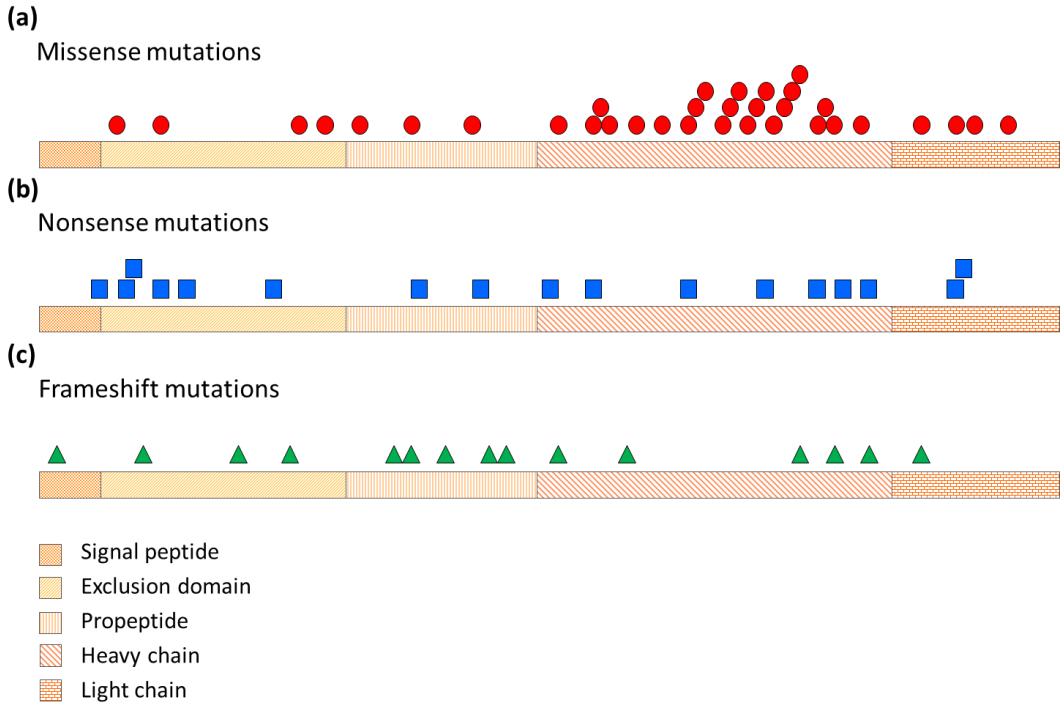

Figure 32. *Distribution of mutations on the cathepsin C protein: (a) missense, (b) nonsense and (c) frameshift.*

Twelve percent (n=9) of all mutations affect the light chain domain, which is important for tetramerization of the mature enzyme: four are missense mutations, two are nonsense variants and one is an in-frame deletion. Three common missense variants, rs151269219, rs28937571 and rs3888798 are also located in this domain (Nakano *et al.*, 2001; Hewitt *et al.*, 2004; de Haar *et al.*, 2005; Noack *et al.*, 2008).

Three percent (n=3) of all mutations are located in the signal peptide region, presumably affecting the translocation or secretion of the protein: one nonsense mutation and one frameshift variant (Lefevre *et al.*, 2001; Hewitt *et al.*, 2004; Kurban *et al.*, 2010).

4.5. Clinical and diagnostic relevance

Historically, Papillon-Lefèvre syndrome was initially considered a variant of Mal de Meleda, due to the similarity of the skin lesions. Subsequently, the two diseases were determined to be different forms of palmoplantar keratodermas (Gorlin *et al.,* 1964). In addition to palmoplantar hyperkeratosis, periodontal inflammation is a main feature of Papillon-Lefèvre syndrome. Clinical diagnosis of Haim-Munk syndrome, an allelic variant of Papillon-Lefèvre syndrome, is based on the presence of arachnodactly, acroosteolysis, pesplanus and onychogryposis in addition to palmoplantar hyperkeratosis and periodontal inflammation (Hart *et al.,* 2000b). Aggressive periodontitis type 1, which can be also considered a variable expression of the Papillon-Lefèvre syndrome phenotype, is characterized by periodontal inflammation and the lack of other symptoms. All the three entities develop as a consequence of *CTSC* mutations. Identification of a *CTSC* mutation gives a definite diagnosis of Papillon-Lefèvre syndrome, Haim-Munk syndrome or aggressive periodontitis type 1 depending on the presented clinical symptoms. In contrast, the absence of *CTSC* mutation suggests a diagnosis of another palmoplantar keratoderma or non-syndromic tooth abnormality.

Analysis of data reported worldwide and the findings of the Hungarian patients with Papillon-Lefèvre syndrome revealed 75 *CTSC* gene mutations. The most frequent mutations are recurrent and are reported both as homozygous and as compound heterozygous. The identification of the most frequent *CTSC* gene mutations has great clinical significance, since they highlight regions of the gene that are important for the development of the disease. The most frequent mutations of the *CTSC* gene and their most common associations are summarized in Table IV. The frequency of mutations, whether looking at the distribution of all mutations or groups of mutations according to type, indicate that exons 5–7, encoding the heavy chain region of the cathepsin C

protein, is the most important region for genetic screening of patients with Papillon-Lefèvre syndrome. Approximately half 53% (n=40) of the all 75 mutations are located within this region. Three types mutations accounted for 93% (n=61) of *CTSC* gene mutations: missense 53% (n=41), nonsense 23% (n=17) and frameshift 17% (n=13). In addition, the majority of missense, nonsense and frameshift mutations occur in exons 5–7.

4.6. Genotype–phenotype correlations

In general, no strict genotype–phenotype correlations have been identified for Papillon-Lefèvre syndrome. Analysis of *CTSC* mutation location (i.e., within or outside the coding regions) suggested that mutations located outside coding regions are more likely to be associated with transgression of the lesions (Hart *et al.,* 2000a), although this hypothesis has not been confirmed (Selvaraju *et al.,* 2003; de Haar *et al.,* 2004; Hewitt *et al.,* 2004). It was also suggested that *CTSC* gene mutations with little functional consequences are putative causes of more common types of early-onset periodontal disease (Hart *et al.,* 2000c), but this observation has also not been confirmed (Hewitt *et al.,* 2004).

Mutations in the *CTSC* gene can lead to the development of Haim-Munk syndrome or aggressive periodontitis type 1 as well as Papillon-Lefèvre syndrome. The common characteristic of these three entities is periodontal inflammation (Hart *et al.,* 2000b; Hewitt *et al.,* 2004; Cury *et al.,* 2005). While all three diseases involve tooth abnormalities, Papillon-Lefèvre syndrome and Haim-Munk syndrome also involve characteristic skin symptoms of palmoplantar hyperkeratosis (Hart *et al.,* 2000b; Hewitt *et al.,* 2004; Cury *et al.,* 2005). Haim-Munk syndrome is further characterized by arachnodactly, acroosteolysis, pesplanus and onychogryphosis (Hart *et al.,* 2000b; Hewitt *et al.,* 2004; Cury *et al.,* 2005).

Several reports indicate that identical mutations of the *CTSC* gene can give rise to multiple different phenotypes: the c.1040A>G p.Tyr347Cys missense mutation can lead either Papillon-Lefèvre syndrome or aggressive periodontitis type 1 (Toomes *et al.,* 1999; Hart *et al.,* 2000c; Hewitt *et al.,* 2004) and the c.145C>T p.Gln49X nonsense

mutation results either in Haim-Munk syndrome or Papillon-Lefèvre syndrome (Selvaraju *et al.*, 2003; Rai *et al.*, 2010). Hart *et al.* (2001) reported that the c.857A>G p.Gln286Arg missense mutation can also contribute to the development of Haim-Munk syndrome and Papillon-Lefèvre syndrome (Hart *et al.*, 2000b). Variable expression of the phenotype associated with the *CTSC* mutation may reflect the influence of other genetic and/or environmental factors (Hart *et al.*, 2000a).

4.7. Future prospects

To date, the comparison of *CTSC* gene mutations has not yet resulted in the identification of genotype–phenotype correlations. Future efforts might provide insight into these correlations and elucidate the mechanism of the different phenotypic variants of Papillon-Lefèvre syndrome. It is necessary to promote both better awareness of the Papillon-Lefèvre syndrome and its phenotypic variants. The availability of the extended clinical findings from *CTSC* mutation carriers is critical for furthering both our understanding of the disease and the development of causative therapies that will be more specific and effective than the symptomatic treatments currently available for patients with Papillon-Lefèvre syndrome and its allelic variants.

5. Summary

In this study, my aim was to investigate Christ-Siemens-Touraine syndrome, Papillon-Lefèvre syndrome and its allelic variants: Haim-Munk syndrome and aggressive periodontitis type 1. The common phenotypic feature of these rare entities is the presence of severe periodontitis. In aggressive periodontitis type 1, there is no further associated symptom, while in Papillon-Lefèvre syndrome and in Haim-Munk syndrome there are some further skin symptoms (Table I.).

Before the huge advances in the development of the sequencing methods these entities based on their clinical symptoms were separated as different diseases. With decoding the human genome in the former decade a lot of disease-causing genetic variations have been discovered. These findings elucidated the genetic background of Christ-Siemens-Touraine syndrome, Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1 and it turned out that they are the results of the mutations in the *EDA1* and *CTSC* genes. Since the same mutation can lead to the development of different phenotypes, it was concluded that Papillon-Lefèvre syndrome, Haim-Munk syndrome and aggressive periodontitis type 1 are not different entities, but the allelic variation of the same disease.

In this study, I have investigated a Hungarian pedigree with Christ-Siemens-Touraine syndrome, two Hungarian pedigrees and two sporadic cases with Papillon-Lefèvre syndrome. Besides complete clinical care including dental and dermatological examinations and interventions, I have initiated the genetic screening and the identification of the underlying causative abnormalities on the *EDA1* and *CTSC* gene. These investigations had great significance for the patients because with the identification of the causative abnormalities family planning can be helped with prenatal diagnostic interventions. In long term, my aim is also to raise the awareness of dentists and other physicians for rare diseases and to create an efficient multidisciplinary team to the clinical workup for these patients.

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7. Electronic database information

Ensemble Genome Browser, (for the wild type sequencing data of the human genome, for the gene variation database regarding disease-causing and non-causing alterations and for the taxonomy analysis of the identified mutation on the GLRA1 gene). www.ensemble.org

Online Mendelian Inheritance in Man, (for the detailed informations on the genetics, inheritance, clinical features and identified mutations in monogenic neurogenetic disorders). www.omim.org

Orphanet Database, (the collection and detailed description of rare diseases). www.orpha.net

UCSC Genome Bioinformatics, (for the design of specific primers used to amplify the sequenced regions of the genes). http://genome.ucsc.edu/

Pubmed, (for the literature search to identify the previously published cases). http://www.ncbi.nlm.nih.gov/pubmed

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Appendix

Publication I

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CONCISE COMMUNICATION

A newly identified missense mutation of the *EDA1* gene in a Hungarian patient with Christ–Siemens–Touraine syndrome

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Abstract Christ–Siemens–Touraine syndrome (CST; OMIM 305100) belongs to the group of ectodermal dysplasias and is characterized by the development of sparse hair, abnormal or missing teeth and sweating deficiency. CST is the consequence of mutations located in the *ectodysplasin A* (EDA1) gene. We have identified a 35-year-old Hungarian man with characteristic dysmorphic facial features, sparse hair, reduced sweating and missing teeth. Direct sequencing of the coding regions revealed a novel missense mutation in the eighth exon (c.971T/A, p.Val324Glu). The affected patient carries the mutation in a hemizygous form. Previous studies reported the association of missense mutations with non-syndromic tooth agenesis. However, the reported hemizygous patient exhibits hypodontia as well as hypotrichosis and reduced sweating. His daughter, an obligate heterozygous carrier of the identified missense mutation, exhibits only mild teeth abnormalities. As the novel missense mutation is located within the tumor necrosis factor (TNF) domain of the ectodysplasin protein, we hypothesize that this genetic variant affects the ectodysplasin/NFκB signaling pathway.

Keywords Christ–Siemens–Touraine syndrome · *EDA1* gene · Missense mutation · TNF domain · NFκB signaling pathway

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Introduction

Ectodermal dysplasia is a heterogeneous group of monogenic disorders that share primary defects in the development of two or more tissues derived from ectoderm or mesoderm [6]. The affected tissues are primarily skin, hair, nails, eccrine glands and teeth [6]. Christ–Siemens–Touraine syndrome—also known as hypohidrotic or anhidrotic ectodermal dysplasia (CST; OMIM 305100)—is characterized by the development of sparse hair (hypotrichosis), abnormal or missing teeth (hypodontia or anodontia), and deficient sweating (hypohidrosis or anhidrosis) [3]. Clinical manifestations of CTS can also include dryness of the skin, eyes, airways and mucous membranes, presumably due to the defective development of several exocrine glands [4]. CTS is also associated with dysmorphic features, such as forehead bumps, rings under the eyes, prominent lips and, occasionally, abnormal nipples [4]. CST is an X-linked, recessive condition, with full expression in males. Some female carriers exhibit no signs of the condition, although many present with tooth malformations, agenesis, or reduced tooth size [12].

CTS develops as a consequence of mutations located in the *ectodysplasin A* (*EDA1*) gene [8, 11]. The ectodysplasin protein belongs to the tumor necrosis factor (TNF) superfamily and influences the NFκB signaling

pathway [5]. The downstream pathway of ectodysplasin/NFκB signaling involves the EDAR membrane-bound receptor and the EDARADD intracellular adaptor [5]. Mutations in the *EDAR* and *EDARADD* genes are associated with autosomal dominant or autosomal recessive forms of hypohidrotic, anhidrotic ectodermal dysplasia phenotype [1, 2]. In addition to these genes, two other genes, including *TRAF6*, that are not involved in the ectodysplasin/NFκB signaling pathway have also been implicated in the development of this phenotype, suggesting other mechanisms in addition to the NFκB signaling pathway [10].

Recently, we have identified a 35-year-old Hungarian man with CTS phenotype, including sparse hair, missing teeth and reduced sweating. The aim of this study was to identify the underlying genetic abnormality of this CTS case.

Materials and methods

Patients

A 35-year-old Hungarian man (II/3) of Transylvanian origin (Sacueni, Transylvania, Romania) was referred to our

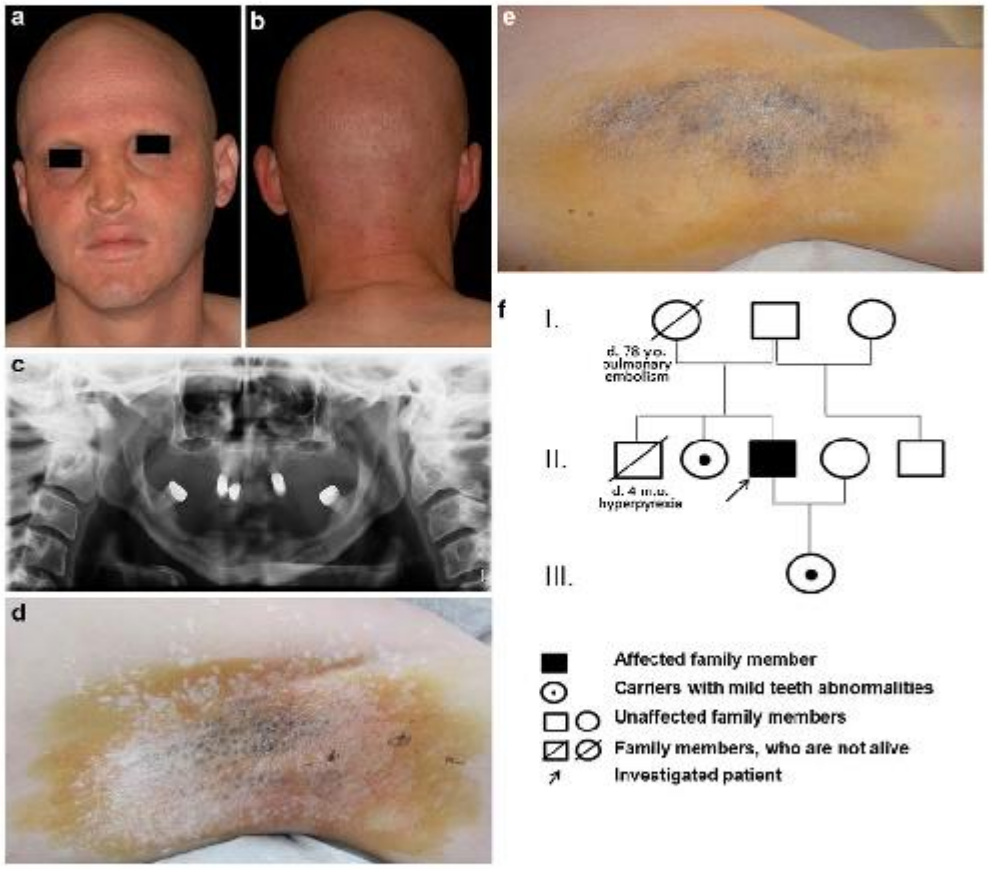

Fig. 1 Clinical symptoms of the investigated patient included: **a** missing eyebrows and eyelashes and **b** sparse hair. **c** A panoramic X-ray photo of the patient demonstrates several missing teeth. The Minor sweat test using starch and iodide showed: **d** reduced sweating in the patient compared to **e** an age- and gender-matched, healthy volunteer. **f** The investigated patient (II/3) is the only family member who exhibits sparse hair, missing teeth and reduced sweating. His sister (II/2) and his daughter (III/1) also have some conical-shaped teeth. Moreover, the older brother of the patient (IV1) died at the age of 4 months due to hyperpyrexia, a symptom of CTS, suggesting he was also affected with CTS

clinic with clinical symptoms of CTS, including missing eyebrows and eyelashes (Fig. 1a), sparse hair (Fig. 1b), missing teeth and reduced sweating. He has seven, permanent, conical-shaped teeth and uses a permanent dental prosthesis (Fig. 1c). In addition to CTS, the clinical diagnosis of atopic dermatitis was also established with a history of dry skin from early childhood. Recently, he also developed itching, excoriated papules and lichenified plaques. On physical examination, he exhibited dysmorphic facial features with frontal bossing, depressed nasal bridge, prominent lips, supraorbital ridges and wrinkled hyperpigmented skin around the eyes. The Minor sweat test using starch and iodide revealed reduced production of sweat (Fig. 1d) compared to an age- and gender-matched, healthy volunteer (Fig. 1e). Reduced sweating of the patient was detected generally in all three investigated regions (armpits, chest and back) and did not show Blaschkoid mosaicism. Detailed history of the patient did not reveal any other relevant chronic diseases. On examination, kidney and liver functions, blood counts and ion levels

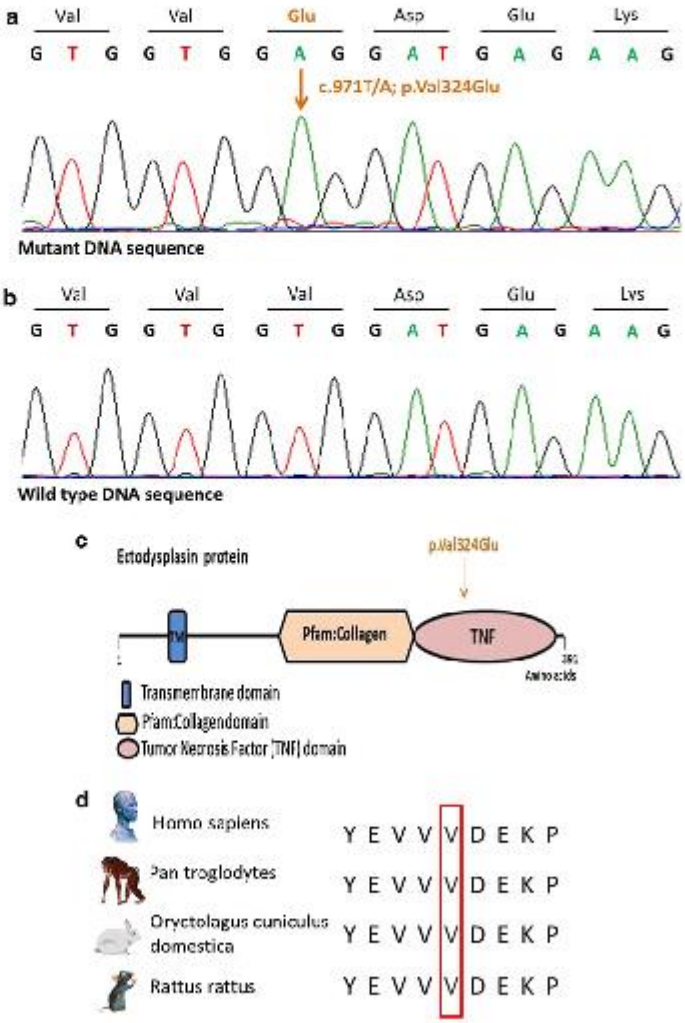

Fig. 2 Direct sequencing of the *EDA1* gene revealed a newly identified missense mutation. **a** The investigated Hungarian patient carried a novel missense mutation (c.971T/A, p.Val324Glu) of the *EDA1* gene in hemizygous form. **b** Investigated healthy controls carried only wild-type sequences. **c** The identified p.Val324Glu missense mutation is located in the TNF domain of the ectodysplasin protein. **d** The identified p.Val324Glu missense mutation is located in a highly conserved region of the ectodysplasin protein

were within normal limits, and total IgE level was slightly elevated (292 IU/ml). The family history (Fig. 1f) revealed that the patient's older brother (II/1) died at the age of 4 months from hyperpyrexia, suggesting the child might have been affected with CTS and experienced severe CTS complications. The patient's older sister (II/2) and the patient's daughter (III/1) have several conical-shaped teeth.

Genetic investigation

Blood samples were taken from the patient and from unrelated controls for genetic investigation. Genomic DNA was isolated with a BioRobot EZ1 DSP Workstation (QIAGEN; Godollo, Hungary). After the amplification of *EDA1* gene coding regions and flanking introns (using primer sequences displayed on the UCSC Genome Browser, http://www.genome.ucsc.edu), DNA sequencing was performed on amplification products.

The investigation was approved by the Internal Review Board of the University of Szeged. Written informed consent was obtained from all donors, and the study was conducted according to the Principles of the Declaration of Helsinki. Unfortunately, due to the geographical distances, the family members of the patient could not provide any material for genetic investigation.

Results

Direct sequencing of eight exons and flanking introns of the *EDA1* gene revealed a novel missense mutation in the eighth exon (c.971T/A, p.Val324Glu; Fig 2). The affected individual carried the mutation in hemizygous form (Fig. 2a), while the unrelated controls ($n = 30$) carried the wild-type sequence (Fig. 2b). This mutation is located in the tumor necrosis factor (TNF) domain of the ectodysplasin protein (Fig. 2c), in a region that is highly conserved evolutionarily among mammals (Fig. 2d).

Discussion

Here, we report a novel hemizygous missense mutation (c.971T/A, p.Val324Glu) of the *EDA1* gene in a Hungarian patient with CTS. It is interesting to note that previous studies have reported missense *EDA1* mutations in non-syndromic tooth agenesis, suggesting that dental tissues are particularly sensitive to ectodysplasin protein abnormalities [7, 9]. These previous findings are in good accordance with our data, as the sister and the daughter of the investigated patient, both of whom are heterozygous carriers of the identified mutation, have some conical-shaped teeth, but exhibit otherwise normal phenotype. Our patient, who is a hemizygous carrier of the mutation, shows full expression of the CTS phenotype with severe dental abnormalities: he developed only seven permanent, conical-shaped teeth and thus currently uses a permanent dental prosthesis. As the novel hemizygous missense mutation (c.971T/A, p.Val324Glu) identified in this report is located in a highly conserved region within the TNF domain of the ectodysplasin protein, we hypothesize that this mutation affects the NFκB signaling pathway.

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Conflict of interest The authors declare that they have no conflict of interest.

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Publication II

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SHORT COMMUNICATION

A novel seven-base deletion of the *CTSC* gene identified in a Hungarian family with Papillon-Lefèvre syndrome

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Abstract Papillon-Lefévre syndrome (PLS; OMIM 245000) is a rare autosomal recessive condition characterized by symmetrical palmoplantar hyperkeratosis and periodontal inflammation, causing loss of both the deciduous and permanent teeth. PLS develops due to mutations in the cathepsin C gene, *CTSC*. Recently we have identified a Hungarian PLS family with two affected siblings. Direct sequencing of the coding regions of the *CTSC* gene revealed a novel seven-base deletion leading to frameshift and early stop codon in the fourth exon of the *CTSC* gene (c.681delCATACAT, p.T188fsX199). The affected family members carried the mutation in homozygous form, while the clinically unaffected family members carried the mutation in heterozygous form. The unrelated controls carried only the wild type sequence. In this paper we report a novel homozygous deletion of seven bases on the *CTSC* gene leading to the development of PLS. Since consanguineous marriage was unknown in the investigated family, the presence of the homozygous seven-base deletion of the *CTSC* gene may suggest that the parents are close relatives.

Keywords Papillon-Lefévre syndrome · Palmoplantar hyperkeratosis · Periodontal inflammation · Cathepsin C gene · Deletion

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Introduction

Papillon-Lefévre syndrome (PLS; OMIM 245000) is a rare autosomal recessive disease, manifesting with symmetrical palmoplantar keratoderma and periodontitis [5]. The keratoderma in PLS may already be present in the first 3 months of life, but in general the palmoplantar hyperkeratosis and the severe periodontitis present simultaneously between 1 and 4 years of age [1]. Besides these symptoms, mild mental retardation, intracranial calcifications as well as hyperhidrosis may occur [1]. The occurence of the disease is 1–4 cases per million; so far approximately 300 cases have been reported worldwide [3]. PLS is the consequence of mutations located in the cathepsin C (*CTSC*) gene. Here we report on a Hungarian PLS pedigree with two affected siblings and the identification of a novel mutation in the *CTSC* gene.

Materials and methods

Patients

A 11-year-old Hungarian girl (Patient I) was referred to our out-patient clinic with a common phenotype of PLS. The

patient was presented with the typical skin symptoms of PLS, complicated with palmoplantar eruption. On referral sharply circumscribed erythema with minimal hyperkeratosis and shedding was seen on both palms (Fig. 1a). The erythema on the plantar surfaces was minimal, however hyperkeratosis with deep fissures dominated (Fig. 1b). These abnormalities first appeared at her age of 19 months. At the age of 4 years, the dermatological findings were also associated with the presence of severe periodontitis, leading to the loss of all deciduous teeth. The other patient (Patient II) was a 2-year-old Hungarian girl, the younger sister of Patient I. She was also referred to our department for having similar symptoms as her older sibling. Palmoplantar eruptions started at the age of 10 months. On referral, minimal erythema was seen on the distal fingertips (Fig. 1c) and erythema with minimal hyperkeratosis was present on the soles of the feet (Fig. 1d). Periodontal inflammation of the deciduous dentition (Fig. 1e) presented together with the dermatologic lesions, although her symptoms were milder compared to that of her older sibling. The symptomless parents reported on a 16-year-old sister of the affected daughters, who has no symptoms (Fig. 1f).

Genetic investigations

Blood samples were taken from the patients and from their clinically unaffected family members as well as from unrelated controls ($n = 130$) for genetic investigation. Genomic DNA has been isolated by a BioRobot EZ1 DSP Workstation (Qiagen; Godollo, Hungary). The coding regions of the *CTSC* gene and the flanking introns were amplified and sequenced (primers were used as displayed on the UCSC Genome Browser www.genome.ucsc.edu).

Results

Direct sequencing of the coding regions and the flanking introns of the *CTSC* gene revealed a novel seven-base deletion in the fourth exon (c.681delCATACAT, p.T188fsX199). This deletion causes frameshift and leads to the development of a premature termination codon (TGA) 32 bases downstream of the mutation. The patients carried the mutation in homozygous form (Fig. 2a), while the unaffected family members carried the same mutation in heterozygous form (Fig. 2b). The unrelated controls carried the wild type sequence (Fig. 2c).

Discussion

The *CTSC* gene encodes cathepsin C, which is a lysosomal cysteine protease responsible for removing dipeptides from the terminus of protein substrates as well as activating many neutrophil serine proteinases. Up to now, approximately 60

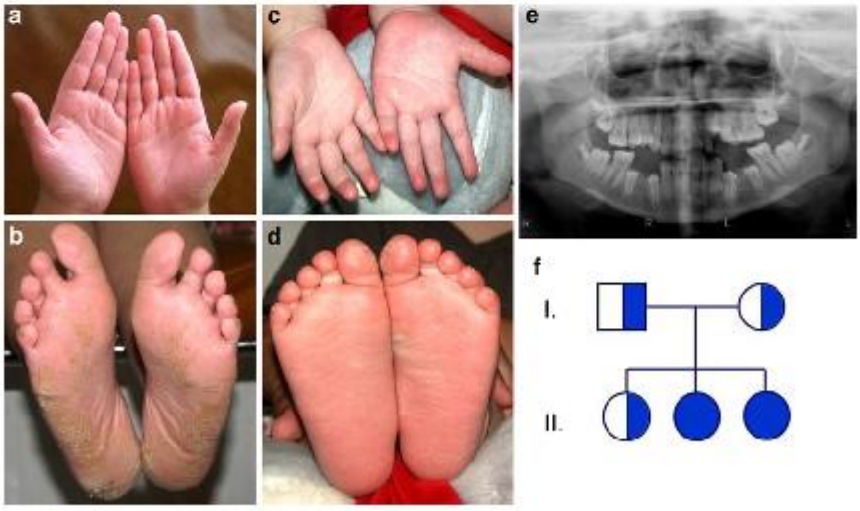

Fig. 1 The pedigree and the skin symptoms of the affected siblings. Hyperkeratosis of the palms (a) and the soles (b) in the case of Patient I. Similar symptoms of the palms (c) and soles (d) in the case of Patient II. X-ray picture of Patient II (e). The investigated Hungarian BSS pedigree spanning two generations and containing two clinically affected and three clinically unaffected family members (f)

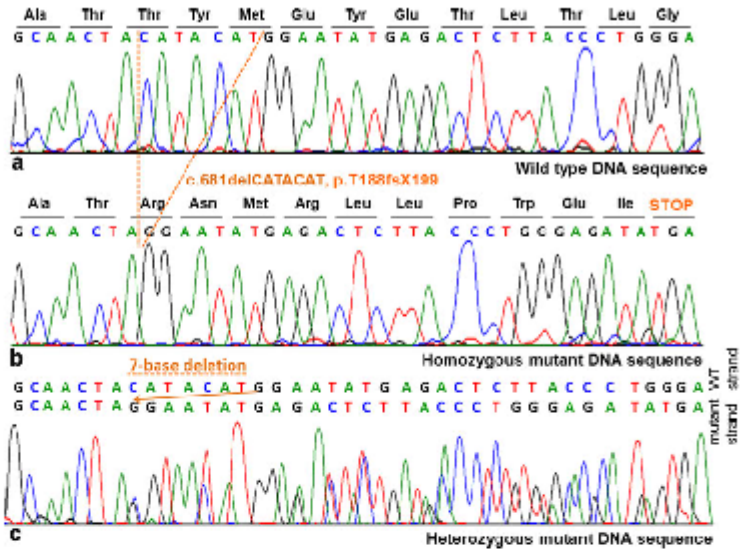

Fig. 2 Identification of a novel mutation of the *CTSC* gene. Direct sequencing revealed a seven-base deletion (c.681delCATACAT, p.T188fsX199) in the fourth exon of the *CTSC* gene. The affected family members carried the deletion in homozygous form (Fig. 2a), while the unaffected family members carried the same deletion in heterozygous form (Fig. 2b). The unrelated controls ($n = 130$) carried the wild type sequence (Fig. 2c)

different mutations have been reported worldwide on the *CTSC* gene [6]. In most of the reported PLS patients, *CTSC* mutations were present in a homozygous form and were the consequences of consanguinity within the family. Functional studies proved that the detected mutations of the *CTSC* gene are loss-of-function mutations, which led to the inactivation of the encoded cysteine protease causing disregulation of the immune response [4]. Periodontal disease and the increased susceptibility to infections have been attributed to impaired neutrophil and T and B cell functions [1, 2].

Here we report on a Hungarian PLS pedigree with two clinically affected siblings. We performed the mutational screening of the *CTSC* gene using direct sequencing and identified a novel, homozygous, seven-base deletion (c.681delCATACAT, p.T188fsX199) in the fourth exon leading to frameshift and premature termination codon at the amino acid position 199. Due to these changes the translated mutant CTSC protein is highly truncated and forms a polypeptide chain of 199 amino acid residues instead of the full length protein with 463 amino acid residues. We hypothesize that this enormous truncation of the mutant CTSC protein may lead to its dysfunction and thus to the development of PLS. The fact that the affected siblings carried the mutation in a homozygous form and the clinically unaffected parents and sibling carried it in a heterozygous form raise the possibility of consanguinity within the affected family. However, the investigated Hungarian pedigree is not aware of any consanguineous marriage in the family, the results may suggest that the parents are somehow close relatives.

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Conflict of interest The authors declare that they have no conflict of interest.

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Publication III

Molecular Genetics & Genomic Medicine

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REVIEW ARTICLE

CTSC and Papillon–Lefèvre syndrome: detection of recurrent mutations in Hungarian patients, a review of published variants and database update

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Keywords
Aggressive periodontitis, *CTSC* gene, Haim–Munk syndrome, Papillon–Lefèvre syndrome

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Abstract

Papillon–Lefèvre syndrome (PLS; OMIM 245000) is an autosomal recessive condition characterized by palmoplantar hyperkeratosis and periodontitis. In 1997, the gene locus for PLS was mapped to 11q14-21, and in 1999, variants in the *cathepsin C* gene (*CTSC*) were identified as causing PLS. To date, a total of 75 different disease-causing mutations have been published for the *CTSC* gene. A summary of recurrent mutations identified in Hungarian patients and a review of published mutations is presented in this update. Comparison of clinical features in affected families with the same mutation strongly confirm that identical mutations of the *CTSC* gene can give rise to multiple different phenotypes, making genotype–phenotype correlations difficult. Variable expression of the phenotype associated with the same *CTSC* mutation may reflect the influence of other genetic and/or environmental factors. Most mutations are missense (53%), nonsense (23%), or frameshift (17%); however, in-frame deletions, one splicing variant, and one 5′ untranslated region (UTR) mutation have also been reported. The majority of the mutations are located in exons 5–7, which encodes the heavy chain of the cathepsin C protein, suggesting that tetramerization is important for cathepsin C enzymatic activity. All the data reviewed here have been submitted to the *CTSC* base, a mutation registry for PLS at http://bioinf.uta.fi/CTSCbase/.

Background

Papillon–Lefèvre syndrome (PLS; OMIM 245000) is a rare form of palmoplantar keratodermas. It was first described by Papillon and Lefèvre (1924). The main characteristic features of PLS are symmetrical palmoplantar hyperkeratosis and periodontal inflammation, causing loss of both the primary and permanent teeth.

Keratoderma in PLS can present in the first 3 months of life, although palmoplantar hyperkeratosis generally first appears in years 1–4 (Haneke 1979). However, several late-onset variants of PLS have also been reported

(Bullon et al. 1993; Pilger et al. 2003). Skin symptoms include transgrediens spread with hyperkeratosis of palms and soles. Diffuse hyperkeratosis is the most commonly observed type; however, the punctuate type occurs rarely. Generally, hyperkeratosis in PLS is not severe (Toomes et al. 1999). Psoriasiform lesions may also develop on the elbows, knees, and knuckles (Toomes et al. 1999). As PLS skin lesions are similar to Mal de Meleda (OMIM 248300) lesions, another rare form of palmoplantar keratodermas, PLS was first considered as a variant of Mal de Meleda. Subsequently, it was determined that the two diseases are different forms of palmoplantar keratodermas (Gorlin et al. 1964).

Periodontitis and gingivitis result in the loss of primary and permanent teeth (Gorlin et al. 1964; Toomes et al. 1999; Hart et al. 2000c; Hewitt et al. 2004a,b). As symptoms appear as the teeth erupt, PLS patients typically report two episodes of gingivitis: the first one at ~3 years of age, leading to the loss of primary teeth (Lundgren and Renvert 2004), the second one at ~15 years of age, resulting in the loss of permanent teeth (Fardal et al. 1998).

In addition to these symptoms, recurrent skin infections and liver abscesses are frequently reported (de Haar et al. 2004; Pham et al. 2004a,b; Romero-Quintana et al. 2013). Moreover, mild mental retardation, intracranial calcifications, and hyperhidrosis can also occur (Haneke 1979). Japanese patients might have an increased risk of developing melanomas at the sites of hyperkeratosis (Nakajima et al. 2008) than other ethnic groups. The prevalence of the disease is 1–4 cases per million and more than 300 cases have been reported worldwide (Gorlin et al. 1964; Haneke 1979). PLS has been reported to occur in a diverse range of ethnic groups and parental consanguinity has been noted in more than 50% of the cases (Gorlin et al. 1964).

PLS is transmitted as an autosomal recessive condition affecting males and females equally. PLS was independently mapped to chromosome 11q14-21 by three groups (Fischer et al. 1997; Laass et al. 1997; Hart et al. 1998). In the mapped region, the causative *cathepsin C* gene (*CTSC*) was independently identified by two groups (Hart et al. 1999; Toomes et al. 1999). The *CTSC*, GenBank accession number NM_001814.4 spans over 46 kb and contains seven exons and six introns (Toomes et al. 1999). According to the Ensemble genome browser (http://www.ensembl.org), this gene has nine splice variants. Of these, five occur in protein coding regions; the remaining four are noncoding transcripts.

CTSC encodes the cathepsin C protein (dipeptidyl-peptidase I), a lysosomal exo-cysteine proteinase belonging to the peptidase C1 family. Cathepsin C is an oligomeric enzyme composed of four identical subunits (Dolenc et al. 1995; Paris et al. 1995). Each subunit contains three different polypeptides – heavy, light, and propeptide chains – which are held together by noncovalent interactions (Cigić et al. 1998). The C-terminus of the propeptide is cleaved upon activation. The residual propeptide is cleaved into two peptides, which are held together by a disulfide bond (Cigić et al. 1998).

Cathepsin C has the ability to remove dipeptides from the amino terminus of proteins and is involved in the zymogen activation of serine proteases. This activity was proposed to play a role in epithelial differentiation and desquamation (Toomes et al. 1999).

In 1999, the first eight mutations of the *CTSC* gene were identified in consanguineous PLS families (Toomes et al. 1999). Since 1999, several reports have described mutations in the *CTSC* gene in different PLS cases from around the world (Table 1). *CTSC* mutations have also been reported in patients with Haim–Munk syndrome (HMS, OMIM 245010), also characterized by palmoplantar hyperkeratosis and periodontal inflammation, as well as arachnodactly, acroosteolysis, pesplanus, and onychogryposis (Hart et al. 2000b). *CTSC* mutations were also found in aggressive periodontitis (AP1, OMIM 170650), which is characterized by severe periodontal inflammation leading to tooth loss without the presence of skin symptoms (Hart et al. 2000c; Hewitt et al. 2004a,b).

To date, a total of 75 mutations have been reported for the *CTSC* gene. The majority of the mutations (97%) were reported in PLS cases, while only a few mutations (3%) were reported in HMS or AP1 cases. Note that some mutations were detected in two different disease entities: c.1040A>G p.Tyr347Cys was reported for AP1 and also for classic PLS families (Toomes et al. 1999; Hart et al. 2000c; Hewitt et al. 2004a,b), c.145C>T p.Gln49X was reported for HMS and for PLS pedigrees (Selvaraju et al. 2003; Rai et al. 2010) and c.857A>G p.Gln286Arg was present in patients either with the HMS or with the PLS phenotype (Hart et al. 2000b). Therefore, PLS, HMS, and AP1 are not different entities; they represent the phenotypic spectrum of a single disease.

Database

A PubMed (http://www.ncbi.nlm.nih.gov/pubmed) literature search was performed to identify all known *CTSC* mutations. In addition, Hungarian pedigrees with PLS were screened for *CTSC* mutations and added to this article. All available information about mutation carriers have been uploaded to the CTSCbase, a mutation registry for PLS (Piirilä et al. 2006). This database is included in the Human Genome Variation Society (HGVS) (www.HGVS.org) list of locus-specific databases. The database can be visited at http://bioinf.uta.fi/CTSCbase/ and has been updated with data from the literature as well as unpublished variants identified in Hungarian PLS pedigrees.

Table 1. Summary of studies reporting *CTSC* gene mutations.

Location	Mutation	Ethnicity	References
5′UTR	c.-55C>A	Slovenian	Kosem et al. (2012)
Exon 1	c.21delG, c.72C>A, c.90C>A, c.96T>G, c.113delCCTG, c.116G>C, c.145C>T	Chinese, French, Indian, Mexican, Moroccan, North African, North American, Puerto-Rican, Thai	Lefèvre et al. (2001), Nakano et al. (2001), Zhang et al. (2002), Allende et al. (2003), Selvaraju et al. (2003), Hewitt et al. (2004a,b), Pham et al. (2004a,b), Nitta et al. (2005), Yang et al. (2007), Kurban et al. (2010)
Exon 2	c.199del24, c.203T>G, c.205C>T, c.267delGG	Brazilian, Chinese, Indian, Mexican	Hart et al. (2000a,b,c), Selvaraju et al. (2003), Pallos et al. (2010), Romero-Quintana et al. (2013)
Exon 3	c.322A>T, c.380A>C, c.386T>A, c.415G>A, c.436delT, c.444insATGT, c.458C>T	Chinese, Egyptian, French, German, Indian, North American, Scotish, Turkish	Hart et al. (2000a,b,c), Lefèvre et al. (2001), Hewitt et al. (2004a,b), Cagli et al. (2005), Yang et al. (2007), Noack et al. (2008a,b), Kobayashi et al. (2013)
Intron 3	c.485-1G>A	Egyptian, Jordanian	Toomes et al. (1999)
Exon 4	c.555G>A, c.566delCATACAT, c.587T>C, c.622insC, c.628C>T, c.629delGA	Algerian, Brazilian, German, Hungarian, Indian, Iranian, Lebanese, Moroccan, Russian, Turkish,	Hart et al. (2000a,b,c, 2002), Cury et al. (2002), Noack et al. (2004, 2008a,b), Cury et al. (2005), Wani et al. (2006), Farkas et al. (2013)
Exon 5	c.704G>A, c.706G>T, c.711del14, c.739A>C, c.745G>T, c.748C>T, c.755A>T, c.756ins130	Algerian, Chinese, Egyptian, Eritrean, Indian, Iranian, North American, Pakistanian, Spanish, Turkish	Toomes et al. (1999), Hart et al. (2000a,b,c), Allende et al. (2001), Lefèvre et al. (2001), Hewitt et al. (2004a,b), Jouary et al. (2008), Wen et al. (2012)
Exon 6	c.778T>C, c.815G>A, c.815G>C, c.851G>A, c.854C>T, c.856C>T, c.857A>G, c.872G>A, c.880T>C	Belgian, Chinese, French, Holland, Indian, Lebanese, Moroccan, North American, Russian, Saudi, Spanish, Sri Lankan, Turkish	Hart et al. (1999, 2000a,b,c), Toomes et al. (1999), Allende et al. (2001, 2003), Lefèvre et al. (2001), Zhang et al. (2002), de Haar et al. (2004), Hewitt et al. (2004a,b), Pham et al. (2004a,b), Yang et al. (2007), Noack et al. (2008a,b)
Exon 7	c.890G>T, c.898G>A, c.899G>A, c.901G>A, c.901G>T, c.902G>T, c.910T>A, c.912C>A, c.923G>A, c.935A>G, c.947T>G, c.956A>G, c.984delTTCTCCA, c.1015C>T, c.1019A>G, c.1028delCT, c.1040A>G, c.1047delA, c.1056delT, c.1131T>G, c.1141delC, c.1156G>C	Egyptian, French, German, Indian, Indian–Pakistanian, Iranian, Japanese, Jordanian, Martinique, North American, Panamanian, Saudi, Sri Lankan, Turkish, Vietnamese	Hart et al. (1999, 2000a,b,c), Toomes et al. (1999), Lefèvre et al. (2001), Nakano et al. (2001), Zhang et al. (2001), Selvaraju et al. (2003), de Haar et al. (2004, 2005), Hewitt et al. (2004a,b), Noack et al. (2004, 2008a,b), Wani et al. (2006), Jouary et al. (2008), Castori et al. (2009), Wen et al. (2012)

Summary of Clinical Findings for Hungarian PLS Patients With Recurrent Mutations

In Hungary, mutation screening for the *CTSC* gene has been available since 2011. Screening is performed with direct sequencing of all coding regions and flanking introns of the *CTSC* gene. Once a putative causative variant was identified in a patient, the available, clinically symptom-free family members and unrelated, healthy control individuals were also investigated.

We have recently identified a Hungarian family with two sisters affected with mild palmoplantar hyperkeratosis and severe periodontitis leading to the loss of all primary teeth. These patients carried the recurrent c.566delCATACAT p.Thr189fsX199 frameshift mutation in a homozygous form (Farkas et al. 2013). An unaffected sister and the parents carried the same mutation in a heterozygous form. The family was not aware of consanguinity. This frameshift mutation has also been previously published for two Moroccan PLS patients presenting variation in the severity of the skin symptoms (Noack et al. 2008a,b).

In another Hungarian family with two sisters presenting severe tooth loss and different degrees of palmoplantar hyperkeratosis (severe and mild), the sisters were found to carry the c.901G>Ap.Gly301Ser missense mutation in a homozygous form (data not published). The family was not aware of consanguinity. This mutation has also been previously published for a German patient with typical PLS skin symptoms (Noack et al. 2008a,b).

In a pair of unrelated Hungarian patients with typical PLS phenotype (a 25-year-old male patient and a 39-year-old female patient), we have identified the

c.748C>Tp.Arg250X homozygous nonsense mutation (data not published). Unfortunately, both of these patients were reared in state care and have no known relatives; therefore, investigation of the family was not possible. The fact that both individuals carry the same mutation raises the possibility that these patients are relatives. This mutation has also been previously published in the literature in a Turkish PLS family (Hart et al. 2000a).

Variants in the *CTSC* Gene

To date, a total of 75 mutations have been identified for the *CTSC* gene, all of which are registered in the CTSC-base. Mutations are named according to HGVS nomenclature guidelines (www.HGVS.org) and numbered with respect to the *CTSC* gene reference sequence (ENSG00000109861 corresponding to the *CTSC* gene transcript ENST00000227266). The 75 unique mutations – point mutations, small deletions, and insertions – are summarized in Figure 1.

Of the reported 75 mutations, 53% are missense ($n = 40$), 23% are nonsense ($n = 17$) and 17% are frameshift ($n = 13$) variants. There are two in-frame deletions, one intronic splice-site variant and one point mutation in the 5′ untranslated region (UTR) of the *CTSC* gene. The majority (75%, $n = 56$) of the mutations has only been reported once. Among these, 65% ($n = 36$) were present in homozygous form in the investigated patients, while 35% ($n = 20$) occurred in a compound heterozygous form. Recurrent mutations (25% of all mutations, $n = 19$) occurred both in homozygous and in compound heterozygous forms and were detected in geographically distant, unrelated families, suggesting mutational clustering on the *CTSC* gene. However, there are reports suggesting that an initial founder effect and subsequent migration of carriers can lead to the presence of the same mutation in geographically distant and unrelated families (Zhang et al. 2001; Kurban et al. 2009).

Known mutations that have been sequenced are unequally distributed on the *CTSC* gene. Half of the

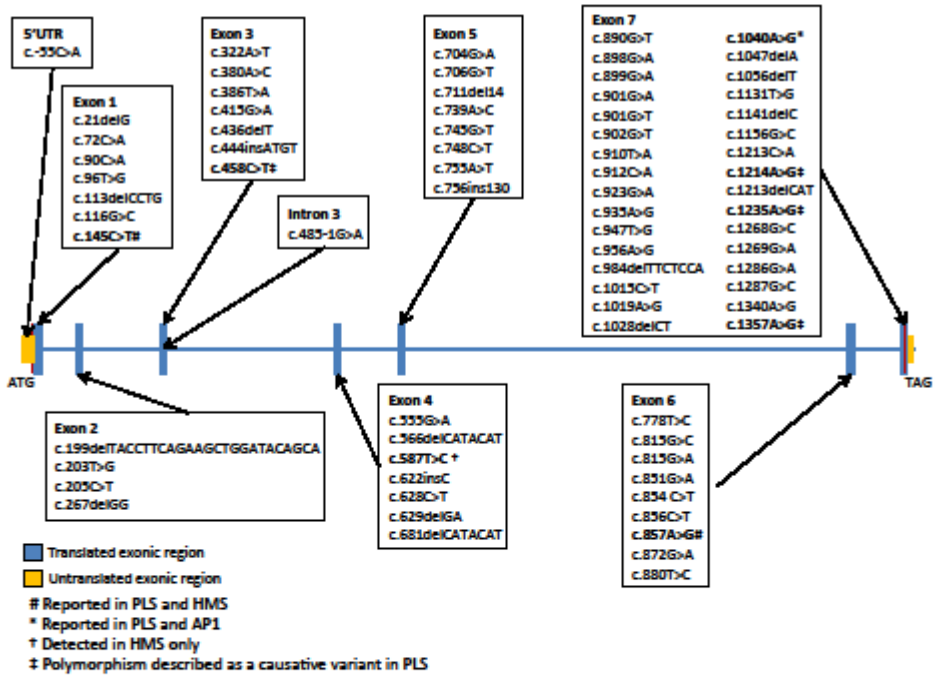

Figure 1. Schematic drawing of the *CTSC* gene, indicating the positions of mutations leading to PLS, HMS, and AP1. Identical mutations can lead to different diseases. The involvement of mutations in specific diseases is indicated as follows: #, PLS and HMS; *, PLS and AP1; †, HMS; ‡, common missense variants reported as causative for PLS.

mutations (53%, $n = 41$) are located within exons 5–7, encoding amino acids 231–394 in the heavy-chain region. Of the remaining half, 16% ($n = 12$) are located within exons 1–3 encoding amino acids 25–134 in the exclusion domain, 12% ($n = 9$) are located within the second half of exon 7 encoding amino acids 395–463 in the light-chain region, 13% ($n = 10$) are located within exon 4 and the first half of exon 5 encoding amino acids 135–230 in the propeptide region, 3% ($n = 2$) are located in the 5′ end of exon 1 encoding amino acids 1–24 in the signal peptide region and 3% ($n = 2$) are located within UTRs. Note, not all mutations have been identified by DNA sequencing.

Homozygous Mutations

To date, 68% of all identified *CTSC* mutations ($n = 75$) were reported in a homozygous form in PLS patients. Of these mutations, 85% ($n = 64$) were present only in homozygous form in PLS patients, while 15% ($n = 11$) were also detected in a compound heterozygous state. Among the homozygous mutations, 50% ($n = 32$) were missense, 25% ($n = 16$) nonsense, 23% ($n = 15$) frameshift mutations, and 2% ($n = 1$) were other types of mutations (Fig. 2A).

Missense Variants

Missense mutations account for approximately half (53%, $n = 41$) of all *CTSC* gene mutations identified to date. Missense mutations occur in all coding regions of the gene; however, the majority occurs in exons 5–7, encoding the heavy-chain region of the cathepsin C protein (Fig. 3A), which is thought to be important for enzyme activity (Turk et al. 2001).

In addition to mutations of the *CTSC* gene, it is important to note that some polymorphisms are common for this gene. For example, the c.458C>T p.Thr153Ile missense variant, which corresponds to variant rs217086, occurs at a residue that is conserved in mammals and is located in the portion of the propeptide that is cleaved upon activation (Hart et al. 2000a). The c.458C>T p.Thr153Ile polymorphism has been indentified in several PLS families, but does not have a causative role in the development of PLS (Allende et al. 2001; Nakano et al. 2001; de Haar et al. 2004; Romero-Quintana et al. 2013).

Further missense variants of the *CTSC* gene reported in PLS families have also been detected as rare polymorphisms as well: c.1214A>Gp.His405Arg corresponds the rs151269219 polymorphism (de Haar et al. 2005; Noack et al. 2008a,b), c.1235A>Gp.Tyr412Cys to the rs28937571 (Hewitt et al. 2004a,b), and c.1357A>Gp.Ile453Val to the rs3888798 polymorphism (Nakano et al. 2001). All of these missense polymorphisms affect the light-chain region of the cathepsin C protein, which is important in the tetramerization of the matured cathepsin C protein. Their eventual pathogenic role should be confirmed or excluded by further studies. It is also possible that these polymorphisms share a common haplotype and are markers of

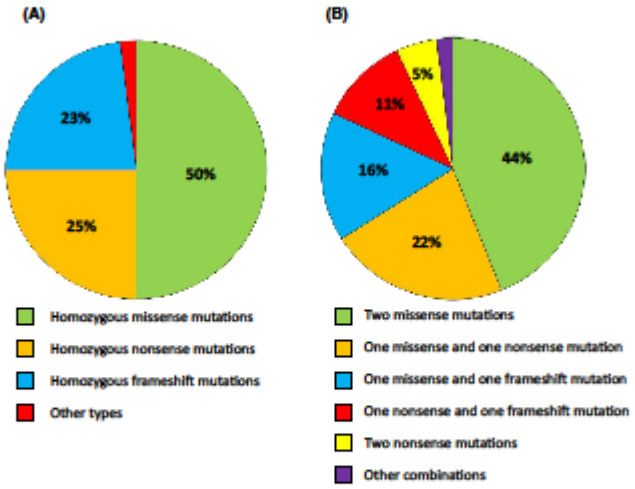

Figure 2. The frequency of mutation types reported for PLS patients in (A) homozygous and (B) compound heterozygous forms.

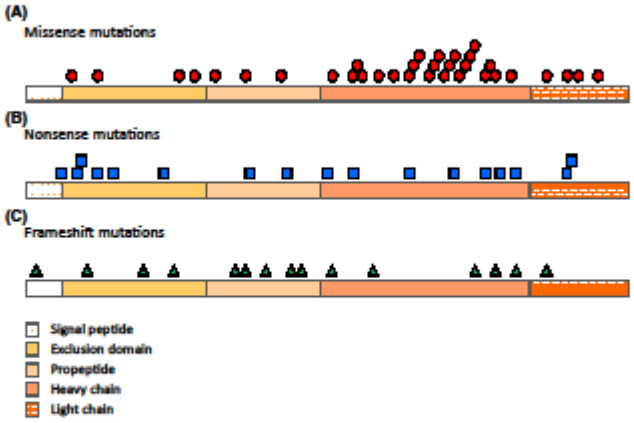

Figure 3. Distribution of mutations on the cathepsin C protein: (A) missense, (B) nonsense, and (C) frameshift.

other underlying, still uncharacterized, genetic abnormalities in these PLS patients.

Nonsense Variants

Nonsense mutations account for 23% ($n = 17$) of the pathogenic mutations identified for the *CTSC* gene to date. Nonsense mutations occur in all coding regions of the gene; however, the majority is located in exons 5–7, encoding the heavy-chain region of the cathepsin C protein (Fig. 3B), which is thought to be important for enzyme activity (Turk et al. 2001).

Frameshift Variants

After missense and nonsense mutations, frameshift mutations of the *CTSC* gene are the most common, accounting for 17% ($n = 13$) of the mutations identified to date. Frameshift mutations occur in all coding regions of the gene; however, the majority is located in exons 4–5 encoding the propeptide region of the cathepsin C protein (Fig. 3C). These mutations might influence the cleavage and the activation processes of the precursor cathepsin C (Turk et al. 2001).

Other Deletions

Two in-frame deletions have been reported in PLS patients. The c.199delTACCTTCAGAAGCTGGATACAGCA deletion corresponding to p.Tyr67_Tyr75del was detected in compound heterozygous form in combination with the c.458C>T missense variant corresponding to p.Thr153Ile (Hart et al. 2000a). This missense mutation is a common polymorphism with no pathogenic role, as determined in subsequent studies (Allende et al. 2001; Nakano et al. 2001; de Haar et al. 2004; Romero-Quintana et al. 2013). The c.1213delCAT p.His405del in-frame deletion was reported in homozygous form in an Indian PLS patient (Wani et al. 2006). A large intragenic deletion of exons 3–7 was observed for another PLS patient in compound heterozygous form, in combination with another missense mutation, c.1156G>C p.Gly386Arg (Jouary et al. 2008).

Splicing Variant

To date, only one pathogenic splice-site mutation has been reported for the *CTSC* gene (Toomes et al. 1999). This single-nucleotide change occurs at the splice-acceptor site (5′ end of exon 3) c.485-1G>A (c.IVS3-1G>A).

UTR Variant

Only one pathogenic mutation has been identified in an UTR of the *CTSC* gene: a single-nucleotide change c.-55C>A at the 5′ end (Kosem et al. 2012). The mutation results in complete loss of *CTSC* mRNA expression and cathepsin C activity (Kosem et al. 2012). In silico analysis suggested that the mutation disrupts the binding sites for AP-2 and Sp transcription factors.

Compound Heterozygous Mutations

To date, 32% ($n = 23$) of all identified *CTSC* mutations ($n = 75$) were detected in a compound heterozygous

form. The most frequent (44%, $n = 10$) compound heterozygotes involved two heterozygous missense mutations. The combination of a heterozygous missense and a heterozygous nonsense mutation occurred in 22% ($n = 5$) of the cases, a heterozygous missense and a heterozygous frameshift mutation in 16% ($n = 4$), a heterozygous nonsense and a heterozygous frameshift mutation in 11% ($n = 3$), and two heterozygous nonsense mutations in 5% ($n = 1$) (Fig. 2B).

Ethnic Variation

PLS has been reported in a diverse range of ethnic groups from all over the world. A quarter (25%, $n = 19$) of the mutations have been reported twice or more in different ethnic groups. One of the most frequently reported missense mutation, the c.815G>Cp.Arg272Pro variant, has been detected in Lebanese, Turkish, Saudi, Holland, Russian and French PLS patients (Toomes et al. 1999; Lefèvre et al. 2001; Zhang et al. 2002; de Haar et al. 2004; Pham et al. 2004a,b; Noack et al. 2008a,b), while another frequent nonsense mutation, c.96T>Gp.Tyr32X, has been observed in PLS patients from Mexico and France (Lefèvre et al. 2001; Zhang et al. 2002; Pham et al. 2004a, b). Moreover, a common frameshift mutation, c.566del-CATACAT p.Thr189fsX200, has been found in Hungarian and Moroccan PLS patients (Noack et al. 2008a,b; Farkas et al. 2013).

Haplotype analyses of different PLS cases carrying identical mutations revealed that these relatively frequent mutations resulted from independent founder events. Two Turkish families carrying the same homozygous nonsense mutation (c.856C>T p.Gln286X exhibited different haplotypes, suggesting that the same mutation arose in the two families independently (Hart et al. 1998, 2000a).

Biological Relevance

Cathepsin C is a lysosomal cysteine protease that was first characterized as an activator of serine proteases from immune and inflammatory cells (Turk et al. 2001). Cell lines derived from cathepsin C-deficient mice fail to activate groups of serine proteases. Unprocessed proteases zymogens included granzymes A, B, and C, cathepsin G, neutrophil elastase, and chymase (Adkison et al. 2002).

The encoded cathepsin C precursor contains 463 amino acids and includes a signal peptide (24 amino acids), an exclusion domain (110 amino acids), a propeptide (96 amino acids), as well as heavy-(164 amino acids) and light-(69 amino acids) chain regions (Turk et al. 2001; Hewitt et al. 2004a,b). Precursor cathepsin C is processed into the mature form by at least four cleavages of the polypeptide (Turk et al. 2001; Adkison et al. 2002). The signal peptide is removed during translocation or secretion of the protein (Turk et al. 2001; Adkison et al. 2002). The exclusion domain is retained in the mature enzyme and separated from the heavy and light chains by excision of a minor C-terminal portion of the propeptide region. The heavy and light chains are also generated by cleavage (Turk et al. 2001; Adkison et al. 2002).

According to a BLAST (http://blast.ncbi.nlm.nih.gov/) search, the cathepsin C protein is highly conserved in vertebrates: the human cathepsin C shows 82% sequence similarity with the sequence from dog, 70% with turkey, and 63% with frog and zebrafish (Fig. 4). The most highly conserved regions are the heavy chain, the light chain, and the C-terminal portion of the exclusion domain, which is thought to be important for enzyme activity.

Half (53%, $n = 40$) of all *CTSC* gene mutations affect the heavy-chain domain and result in different positioning of its N-terminus. As the N-terminal region is involved in oligomer contacts with the N-terminal region of the light chain, the mutation may interfere with tetramer formation (Turk et al. 2001). This finding indicates that tetramerization of the cathepsin C enzyme is crucial for its function. The majority of the two most common types of *CTSC* mutations (missense and nonsense) affect this domain (Fig. 3A and B).

Sixteen percent ($n = 12$) of all *CTSC* mutations affect the exclusion domain, which blocks access to the active site and prevents substrates from binding any part except their N-termini. Thirteen mutations were detected in the exclusion domain; of these, six are nonsense variants, four are missense mutations, and three are deletions (two resulting in frameshift and one in an in-frame deletion).

Thirteen percent ($n = 10$) of all *CTSC* gene mutations affect the propeptide fragment, which plays a pivotal role in the activation of the cathepsin C precursor. The majority of frameshift mutations are located in this domain (Fig. 3C).

Twelve percent ($n = 9$) of all mutations affect the light-chain domain, which is important for tetramerization of the mature enzyme: four are missense mutations, two are nonsense variants and one is an in-frame deletion. Three common missense variants, rs151269219, rs28937571, and rs3888798 are also located in this domain (Nakano et al. 2001; Hewitt et al. 2004a,b; de Haar et al. 2005; Noack et al. 2008a,b).

Three percent ($n = 3$) of all mutations are located in the signal peptide region, presumably affecting the translocation or secretion of the protein: one nonsense mutation and one frameshift variant (Lefèvre et al. 2001; Hewitt et al. 2004a,b; Kurban et al. 2010).

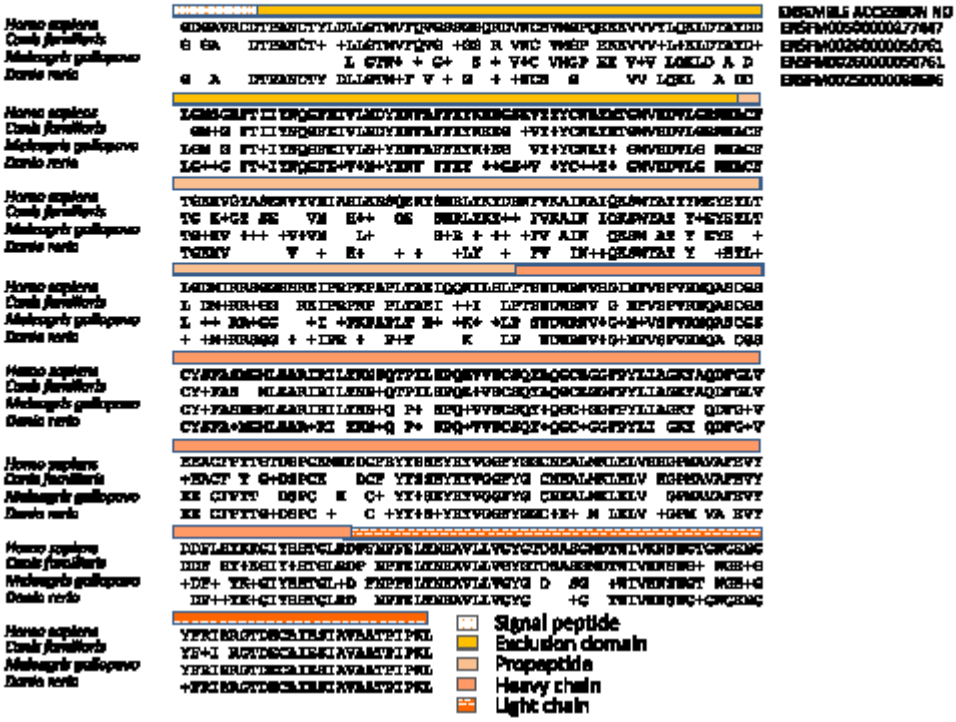

Figure 4. Conservation of cathepsin C protein sequence in vertebrates.

Clinical and Diagnostic Relevance

Historically, PLS was initially considered a variant of Mal de Meleda, due to the similarity of the skin lesions. Subsequently, the two diseases were determined to be different forms of palmoplantar keratodermas (Gorlin et al. 1964). In addition to palmoplantar hyperkeratosis, periodontal inflammation is a main feature of PLS. Clinical diagnosis of HMS, an allelic variant of PLS, is based on the presence of arachnodactly, acroosteolysis, pesplanus, and onychogryposis in addition to palmoplantar hyperkeratosis and periodontal inflammation (Hart et al. 2000b). AP1, which can be also considered a variable expression of the PLS phenotype, is characterized by periodontal inflammation and the lack of other symptoms. All the three entities develop as a consequence of *CTSC* mutations. Identification of a *CTSC* mutation gives a definite diagnosis of PLS, HMS, or AP1 depending on the presented clinical symptoms. In contrast, the absence of *CTSC* mutation suggests a diagnosis of another palmoplantar keratoderma or nonsyndromic tooth abnormality.

Analysis of data reported for Hungarian PLS patients revealed 75 *CTSC* gene mutations. The most frequent mutations are recurrent and are reported both as homozygous and as compound heterozygous. The identification of the most frequent *CTSC* mutations has great clinical significance, as they highlight regions of the gene that are important for the development of the disease. The most frequent mutations of the *CTSC* gene and their most common associations are summarized in Table 2. Approximately half 53% ($n = 40$) of the all 75 mutations are located within exons 5–7, encoding the heavy-chain region of the cathepsin C protein. Three types mutations accounted for 93% ($n = 61$) of *CTSC* gene mutations: missense 53% ($n = 41$), nonsense 23% ($n = 17$), and frameshift 17% ($n = 13$). In addition, the majority of missense, nonsense, and frameshift mutations occur in exons 5–7.

Table 2. The most frequent compound heterozygous pathogenic combinations of *CTSC* mutations.

Mutation on Allele 1	Mutation type	Mutation on Allele 2	Mutation type	References
c.96T>G p.Tyr32X	Nonsense	c.380A>C p.His127Pro	Missense	Lefèvre et al. (2001), Zhang et al. (2002), Pham et al. (2004a,b)
		c.815G>A p.Arg272His	Missense	
c.322A>T p.Lys108X	Nonsense	c.436delT p.Ser146fsX30	Frameshift	Noack et al. 2008a,b
		c.504C>G p.Tyr168X	Nonsense	
c.415G>A p.Gly139Arg	Missense	c.72C>A p.Cys24X	Nonsense	Hewitt et al. (2004a,b), Cagli et al. (2005), Yang et al. (2007)
		c.706G>T p.Asp236Tyr	Missense	
		c.778T>C p.Ser260Pro	Missense	
		c.1141delC p.Leu381fsX13	Frameshift	
c.706G>T p.Asp236Tyr	Missense	c.415G>A p.Gly139Arg	Missense	Allende et al. (2001), Hewitt et al. (2004a,b)
		c.872G>A p.Cys291Tyr	Missense	
c.815G>C p.Arg272Pro	Missense	c.96T>G p.Tyr32X	Nonsense	Toomes et al. (1999), Lefèvre et al. (2001), Zhang et al. (2002), de Haar et al. (2004), Pham et al. (2004a,b), Noack et al. (2008a,b)
		c.1141delC p.Leu381fsX13	Frameshift	
c.1141delC p.Leu381fsX13	Frameshift	c.415G>A p.Gly139Arg	Missense	Lefèvre et al. 2001
		c.815G>C p.Arg272Pro	Missense	

Genotype–Phenotype Correlations

In general, no strict genotype–phenotype correlations have been identified for PLS. Analysis of *CTSC* mutation location (i.e., within or outside the coding regions) suggested that mutations located outside coding regions are more likely to be associated with transgression of the lesions (Hart et al. 2000a), although this hypothesis has not been confirmed (Selvaraju et al. 2003; de Haar et al. 2004; Hewitt et al. 2004a,b). It was also suggested that *CTSC* gene mutations with little functional consequences are putative causes of more common types of early-onset periodontal disease (Hart et al. 2000c), but this observation has also not been confirmed (Hewitt et al. 2004a,b).

Mutations in the *CTSC* gene can lead to the development of HMS or AP1 as well as PLS. The common characteristic of these three entities is periodontal inflammation (Hart et al. 2000b; Hewitt et al. 2004a,b; Cury et al. 2005). While all three diseases involve tooth abnormalities, PLS and HMS also involve characteristic skin symptoms of palmoplantar hyperkeratosis (Hart et al. 2000b; Hewitt et al. 2004a,b; Cury et al. 2005). HMS is further characterized by arachnodactly, acroosteolysis, pesplanus, and onychogryphosis (Hart et al. 2000b; Hewitt et al. 2004a,b; Cury et al. 2005).

Several reports indicate that identical mutations of the *CTSC* gene can give rise to multiple different phenotypes: the c.1040A>G p.Tyr347Cys missense mutation can lead either PLS or AP1 (Toomes et al. 1999; Hart et al. 2000c; Hewitt et al. 2004a,b) and the c.145C>T p.Gln49X nonsense mutation results either in HMS or PLS (Selvaraju et al. 2003; Rai et al. 2010). Hart et al. (2000b) reported that the c.857A>G p.Gln286Arg missense mutation can also contribute to the development of HMS and PLS (Hart et al. 2000b) (Fig. 1). Variable expression of the phenotype associated with the *CTSC* mutation may reflect the influence of other genetic and/or environmental factors (Hart et al. 2000a).

Future Prospects

To date, the comparison of *CTSC* gene mutations has not yet resulted in the identification of genotype–phenotype correlations. Future efforts might provide insight into these correlations and elucidate the mechanism of the different phenotypic variants – PLS, HMS, and AP1 – of the disease. We believe that, to improve molecular analysis of the *CTSC* gene, it is necessary to promote both better awareness of the PLS, HMS, and AP1 phenotypic variants of the same disease and better understanding of the underlying molecular mechanisms. The availability of the extended clinical findings from *CTSC* mutation carriers, as provided by the CTSCbase, is critical for furthering both our understanding of the disease and the development of causative therapies that will be more specific and effective than the symptomatic treatments currently available for patients with PLS, HMS, and AP1 variants.

Acknowledgments

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Conflict of Interest

None declared.

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Rekurrens európai misszensz mutáció egy magyar Papillon–Lefèvre szindrómában szenvedő családban

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A Papillon–Lefèvre szindróma egy autoszomális recesszív öröklődést mutató ritka betegség, melyet agresszív periodontitis és palmoplantáris keratoderma jellemez. A betegség kialakulásáért a cathepsin C gén mutációi a felelősek. A szerzők vizsgálatainak célja egy magyar Papillon–Lefèvre szindrómában szenvedő testvérpár klinikai tüneteinek részletes bemutatása és a betegség hátterében álló mutáció meghatározása volt. A testvérek már tüneteik megjelenése óta rendszeres fogászati és bőrgyógyászati gondozás alatt állnak, de mivel a Papillon–Lefèvre szindróma genetikai vizsgálatára Magyarországon csak egy-két éve van lehetőség, így a genetikai vizsgálatukra csak most került sor. Szerzők vizsgálataik során egy homozigóta misszensz mutációt azonosítottak a cathepsin C génen, mely már az irodalomból ismert: korábban egy német Papillon–Lefèvre szindrómában szenvedő családban azonosították. Vizsgálataik bemutatásával szeretnék felhívni a figyelmet egy ritka betegségre, az első tünetként gyakran agresszív periodontitisszel jelentkező Papillon–Lefèvre szindrómára, és arra, hogy a körképben immár hazánkban is elérhető a genetikai vizsgálat. Ennek egyes esetekben a gyermekvállalás és a családtervezés során lehet nagy jelentősége.

Kulcsszavak: Papillon–Lefèvre szindróma, cathepsin C gén, agresszív periodontitis, palmoplantáris keratoderma, mutáció

Bevezetés

A Papillon–Lefèvre szindróma (OMIM 245 000) egy ritka, autoszómális recesszív öröklődést mutató betegség, melynek jellegzetes tünetei a gyors lefolyású, destruktív fogágy-gyulladás és szimmetrikus tenyéri, talpi hyperkeratosis [21]. A Papillon–Lefèvre szindrómát 1924-ben írta le elsőnek Paul-Henri Papillon és Paul Lefèvre [44]. A kialakuló gyors progressziójú destruktív periodontitis a tejfogak és a maradó fogak korai elvesztését eredményezi [21, 25, 54], bár az utóbbi két évtizedben számos szerző számolt be sikeres terápiáról, amelyek arról szólnak, hogy hosszú távon sikerül megelőzni a további tapadásveszteséget és fogelvesztést [16, 41, 42, 53, 58].

A Papillon–Lefèvre szindrómában szenvedő betegeknél a fogászati tünetek először kb. 3 éves korban jelentkeznek [18, 24, 26], bár leírtak korábbi kezdetet is (másfél éves kor) [47]. A betegség gyors lefolyását jelzi, hogy négy-öt éves korban már kifejezett csontpusztulás, súlyos gyulladás, fogmozgathatóság, recesszió, furkációérintettség (tejfog!), tályogképződés, szájbűz tapasztalható [9, 12, 15, 24, 51], a betegek egy része már ebben a korban elveszítheti tejfogait [2, 15]. A maradófogak is hamar érintetté válnak [15, 24], főleg, ha a tejfogak elvesztése nem előzi meg az erupciót [14]. A maradó fogak károsodása és elvesztése is gyorsan történik, legkésőbb felnőtt korukra a páciensek fogatlanná válhatnak parodontológiai kezelés ellenére is [15, 33, 56], főleg a nem kooperáló vagy a fenntartó terápiát elmulasztó betegek [42].

A változatos súlyosságú, általában szimmetrikus, tenyéri és talpi lokalizációt mutató börtünetek akár már a megszületést követően nem sokkal [6, 11, 15, 24], de legkésőbb egy- és négyéves kor között jelentkeznek [22].

A betegség klasszikus tünetei mellett ritkábban előfordulhatnak még visszatérő bőrfertőzések, májtályog, vesetályog, neoplazma az érintett bőrterületen, szem inhártyáján, enyhe mentális retardáció, koponyán belüli meszesedés és esetleg fokozott izzadás is [4, 13, 27, 37, 38, 46, 49]. A kísérőbetegségek közül leírtak gyors lefolyású, fatális kimenetelű elváltozásokat is okoztak, amely gyermek illetve serdülőkorban vezetett halálhoz: májtályog következtében kialakuló szeptikus shock illetve dilatációs cardiomyopathia okozta a páciensek elvesztését [28, 31].

A betegség előfordulása meglehetősen ritka, eddig mintegy 300 esetet közöltek világszerte, a prevalenciáját 1-4:1000000-ra becsülik [21; 22]. A Papillon–Lefèvre szindróma kialakulásának hátterében a cathepsin C gén mutációi állnak, eddig mintegy 75 mutációt azonosítottak a génen [39]. A cathepsin C gén mutációi eredményezik továbbá a Haim-Munk szindrómát (OMIM 24 5010)

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1. táblázat

A cathepsin C gén mutáció által okozott, korábban külön kórképeknek tekintett, ma már a Papillon–Lefèvre szindróma variánsainak tartott tünetegyüttesek bemutatása

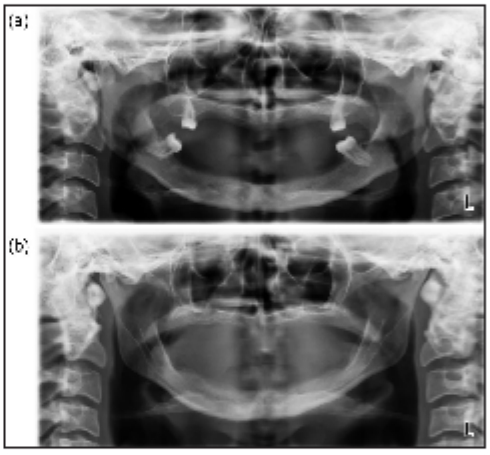
	Papillon–Lefèvre szindróma	Haim-Munk szindróma	Agresszív parodontitis 1-es típus
OMIM azonosító	245000	245010	170650
Klinikai tünetek			
Parodontitis	√	√	√
Palmoplantaris keratoderma	√	√	x
Pes planus	x	√	x
Onychogryphosis	x	√	x
Arachnodactilia	x	√	x
Acroosteolysis	x	√	x
Genetikai háttér			
Cathepsin C mutációk	√	√	√

és az agresszív periodontitis 1-es típusát (OMIM 17 0650), melyeket ma már nem külön entitásnak, hanem a Papillon–Lefèvre szindróma eltérő súlyosságú variánsainak tekintenek *(1. táblázat)* [23, 25]. A továbbiakban egy magyar Papillon–Lefèvre szindrómában szenvedő testvérpár klinikai tüneteit, illetve a betegség hátterében álló mutáció azonosítását mutatjuk be részletesen.

Betegek és módszerek

A jelenleg 29 és 24 éves lánytestvérek már tüneteik kialakulása óta fogászati és bőrgyógyászati gondozás alatt állnak. A lánytestvérek esetében a bőrgyógyászati tünetek alakultak ki először. A betegségre jellemző gyors progressziójú, generalizált periodontitis miatt, mindkét beteg esetében kezdetben a tejfogak korai elvesztése, később a maradófogak érintettsége és elvesztése jelentkezett (csak a fiatalabb testvérnek maradt meg négy bölcsességfoga) *(1. ábra)*. A bőrtünetek a nagyobb testvérnél megszületését követően rögtön, húgánál kb. kétéves korában jelentkeztek. Kezdetben a talpakon bőrpír, majd lemezes hámló elváltozás alakult ki. Ötéves korban a tenyér, egy-két évvel később a térdkalács és könyök körüli bőrterület is érintett lett. A tenyereken bőrszárazság és enyhe rajzolatfokozódás, míg a talpakon közepes súlyosságú hyperkeratosis alakult ki mindkét beteg esetében *(2. ábra)*. Ahogy az ábrán is látható és az anamnézisük is megerősíti, a kisebbik testvér fogászati és bőrtünetei később és enyhébb formában jelentkeztek-jelentkeznek.

A betegek fogászati és bőrgyógyászati gondozása mellett genetikai kivizsgálást végeztünk a háttérben álló mutáció azonosítása céljából. A genetikai vizsgálathoz előzetes tájékoztatást és írásbeli beleegyezést követően vért vettünk, majd genomi DNS-t izoláltunk. A DNS-en specifikus primerek segítségével a cathepsin C gén kódoló szakaszait PCR reakciók során felszaporítottuk, majd a PCR termékek direkt szekvenálása történt meg

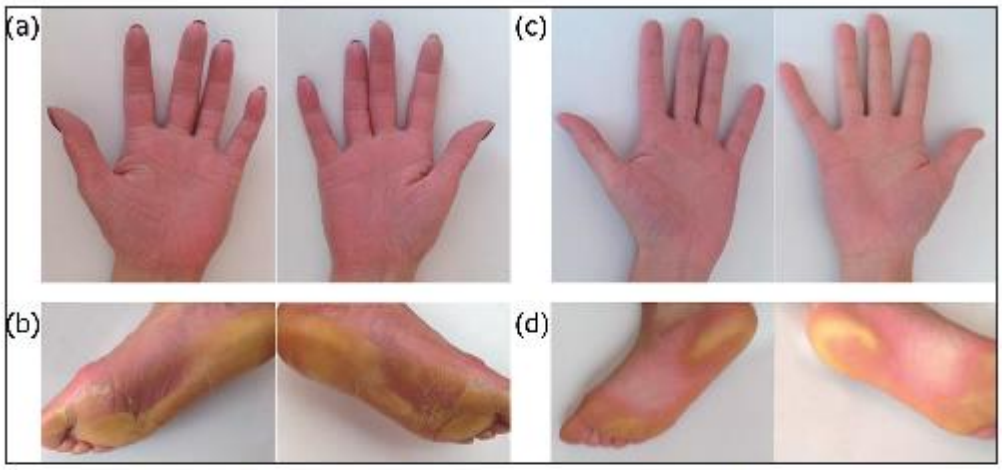


1. ábra: A fogászati tüneteket bemutató orthopantomogramok: (a) a 29 éves és (b) a 24 éves beteg esetében

mutációszűrés céljából. Az alkalmazott módszerek részletes leírása megtalálható a *Farkas és mtsai* (2013) közleményben [19].

Eredmények

Az elvégzett genetikai vizsgálatink során a vizsgált Papillon–Lefèvre szindrómában szenvedő testvérpár mindkét tagjában egy homozigóta misszensz mutációt azonosítottunk (c.901G/A p.Gly301Ser). A mutáció a cDNS 901-es pozíciójában egy guanin adenin báziscserét eredményez, mely következtében a fehérjén a 301-es pozícióban egy glicin-szerin aminosavcsere alakul ki *(3. ábra)*. A vizsgált betegek családalapítás előtt állnak, ezért a párjaik genetikai vizsgálata is megtörtént, akiknél mu-



2. ábra: A bőrgyógyászati tünetek: a 29 éves beteg (a) tenyéri és (b) talpi tünetei, a 24 éves beteg (c) tenyéri és (d) talpi tünetei

tációt heterozigóta hordozói státuszban sem azonosítottunk. Tehát a vizsgált betegek és párjaik leendő gyermekei ugyan az azonosított mutációt heterozigóta formában hordozni fogják, de klinikailag egészségesek lesznek. Az azonosított misszensz mutáció egy, az irodalomból már ismert mutáció, melyet korábban német Papillon–Lefèvre szindrómában szenvedő betegeknél írtak le először [43].

Megbeszélés

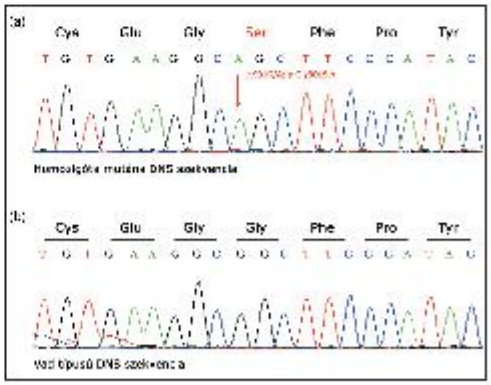
A Papillon–Lefèvre szindróma egy agresszív periodontitissel és tenyéri talpi fokozott elszarusodással járó ritka betegség. Vizsgálataink során egy magyar Papillon–Lefèvre szindrómában szenvedő testvérpár genetikai vizsgálatának eredményeit és kórtörténetét mutatjuk be.

A testvérpár esetében a betegség első tünete, már megszületésüket követően a talpon jelentkező bőrelváltozások voltak, amelyeket 5 éves koruktól a kézen, majd egy-két évvel később a térdkalácsot borító bőrfelület eltérései követtek. A fogászati tünetek korán jelentkeztek, az idősebb testvér 4 éves korában tejfogainak nagy részét elvesztette, húgánál ebben az időben alakult ki súlyos inygyulladás és tapadásveszteség [8].

Jellemzően, mind a bőr-, mind a fogászati tünetek az idősebb testvérnél manifesztálódtak korábban és súlyosabb formában. A tünetek családi halmozódása utalt először arra, hogy valamely ritka, genetikailag meghatározott formáról van szó. A Papillon–Lefèvre szindróma diagnózisát a klinikai tünetek alapján állították fel, genetikai vizsgálatot ekkor még nem végeztek. A testvérpár három évig járt fenntartó terápiára klinikánkra, utána nem jelentkeztek.

Az elmúlt év áprilisában, egy évvel ezelőtt keresték fel Intézetünket ismételten. Az idősebbik testvér ekkor már 10 éve teljesen fogatlan volt, börtünetei kifejezettek jelenleg is. A fiatalabb testvér négy bölcsességfoga maradt szájban, amelyek mellett tasak nem szondázható, inyszél gyulladásmentes. Ő is 18 éves korára vesztette el többi maradó fogát. Börtünetei enyhék, jelentős panaszt nem okoznak. OPT felvételen mindkét esetben jelentős involúció figyelhető meg. Mindketten teljes lemezes kivehető pótlást viselnek, amellyel megfelelően tudnak étkezni és beszédjükben sem zavarja őket.

Az elvégzett genetikai vizsgálattal és a háttérben álló mutáció azonosításával a klinikai gyanú teljes mértékben megalapozottá vált. A genetikai vizsgálatokkal nem a diagnózis igazolása történt meg, hanem a fiatal felnőtt, tünetekkel rendelkező testvéreket és párjaikat a családtervezésben is segítettük.



3. ábra: A genetikai vizsgálati eredmények: (a) az azonosított homozigóta misszensz mutáció, (b) vadtípusú szekvencia

Általánosságban elmondható, hogy a Papillon–Lefèvre szindróma fogászati tünetei nem befolyásolják a tejfogak megjelenést, azonban kialakulásukat követően súlyos gingivitis és periodontális destrukció alakul ki [15, 29]. A hagyományos kezelési eljárások nem képesek megállítani ezeket a folyamatokat, melyek végül a tejfogak idő előtti – 4 éves kor körül bekövetkező – elvesztését eredményezik. A gingivitis a fogak elvesztését követően elmúlik, majd a maradandó fogak áttörését követően ismételten kialakul [15, 29]. A gingivitis és a periodontális destrukció pedig a maradandó fogak esetében is azok korai elvesztését eredményezhetik [15, 29].

Az elmúlt húsz évben számos közlemény jelent meg, amely hosszú távú (5-13 év), eredményes kezelésről számol be. Radikális parodontális terápia, a teljes száj dezinfekciója és szigorú fenntartó terápia segít a betegség progressziójának megelőzésében vagy lassításában [36, 41, 42, 53, 58]. A terápia kulcsa, a parodontopatogén baktériumok, elsősorban az Aggregatibacter actinomycetemcomitans eliminálása és reinfekciójának megakadályozása [26, 47]. Kombinált mechanikai biofilm eltávolítás és antibiotikus terápia (250 mg amoxicyllin és 250 mg metronidazol, naponta háromszor, 7–10 napig) mutatkozik eredményesnek. Rossz szájhigiéniával rendelkező, motiválatlan páciens antibiotikus kezelése vagy monoterápia sikertelensége, az Aggregatibacter actinomycetemcomitans reinfekcióját, rezisztens törzsek szelekcióját eredményezheti [14, 30]. Az eredményes terápia feltétele az előírt gyógyszeres kezelés szigorú betartása, professzionális és egyéni szájhigiéniás módszerek megfelelő elvégzése együttesen [56].

Jó hatású a tejfogak és a súlyos tapadásveszteséget elszenvedett fogak korai eltávolítása. Annak ellenére, hogy a maradó fogak áttörése előtt történő tejfog extractio a dentális és szkeletális fejlődés eltéréseivel jár [7], a megfelelően motivált és parodontálisan kezelt páciensek esetében ezek az elváltozások sikeresen kezelhetők fogszabályozással, anélkül, hogy a fogak további parodontális károsodást szenvednének [36, 42, 58], viszont eredményesen eliminálhatók a parodontopatogén baktériumok, így az Aggregatibacter actinomycetemcomitans is [12, 41, 47, 51]. Mivel több adat utal arra, hogy a parodontopatogén baktériumokkal a családtagok megfertőzhetik egymást, sőt a háziállatokat (kutyát) is [45, 48, 57], többen az együtt élő hozzátartozókra (kutyára) is kiterjesztették az anti-infektiv terápiát [42, 48, 55]. A konzervatív parodontológiai kezelés – teljes száj dezinfekció – mellett, lebenyes tasakműtét alkalmazása is szükségessé válhat [2, 50]. Szigorú fenntartó terápia (6 hét–3 hónap) mellett értek el jó eredményeket [16, 35, 36, 41, 58].

A fogatlanná vált páciensek rehabilitációjára dentális implantációt és a hozzá szükséges csontpótlást is alkalmaztak. A közleményekben leírt esetek követési ideje általában egy év [3, 17, 55, 59], de a hosszabb távú, sikeres eseteknél sem több mint 3-4, 5 év [1, 52, 56]. A fenntartó terápia elmulasztása fogágybetegségben nem szenvedő pácienseknél is peri-implantáris gyulladáshoz vezet, amelynek a kockázatát a maradék fogazat parodontális gyulladása tovább fokozza [10], ez Papillon–Lefèvre szindrómában tovább emeli a rizikót: nem kooperáló vagy a fenntartó terápiát kihagyó pácienseknél 4 év után peri-implantáris mucositis, négyből három páciensnél pedig peri-implantitis alakult ki az előzőleg behelyezett műgyökerek mellett, egy páciensnél az összes implantátum mellett [42].

A bőrtünetek leggyakrabban tenyéri-talpi lokalizációt mutatnak, szimmetrikusak és a tenyéri, illetve a talpi felszínről a kézhátra, a lábhátra és a sarkakra terjedhetnek [11]. A tenyerek és a talpak mellett a könyökökön és a térdeken is kialakulhatnak pikkelysömörre emlékeztető, fokozott elszarusodást mutató plakkok [11]. A betegeknél jelentkezhetnek visszatérő bőrfertőzések, bőrtályogok is. A bőrtünetek súlyossága változatos lehet az igen enyhe mértékűtől a súlyosig.

A bőrtünetek esetében orális retinoid – acitretin, isotretin – kezelés hatásos lehet, melyet a maradandó fogak kialakulásának időszaka alatt, illetve ha a bőrtünetek súlyossága megkívánja, akkor hamarabb javasolt alkalmazni. [5]. Bár több szerző szerint a retinoid kezelés a parodontológiai tüneteket is enyhíti [5, 20, 40], a parodontológiai és mikrobiológiai paraméterek részletes monitorizálását tartalmazó közlemények ezt nem tudták alátámasztani [14, 34, 42]. A retinoid terápia mellékhatásai miatt (csontfejlődési zavar – epiphysis porc idő előtti csontosodása, májfunkciós értékek romlása, bőr- és nyálkahártya kiszáradása) a szer alkalmazása elővigyázatosságot kíván [32]. A bőrelváltozások és a fogazat károsodásának mértéke nem függ össze [34, 56], és ahogy mi is tapasztaltuk, a testvérek között a különböző tünetek eltérő súlyossággal fordulhatnak elő [24, 51], valamint a terápiára is eltérő módon reagálhatnak [14].

Vizsgálataink jelentősége, hogy felhívják a figyelmet egy ritka betegségre, a Papillon–Lefèvre szindrómára, melynél a kialakuló első tünetek a fogászati tünetek is lehetnek. Továbbá vizsgálatainkkal a genetikai vizsgálatok jelentőségét is hangsúlyozzuk, mellyel elősegíthető, hogy az érintett családok esetében egészséges utódok születhessenek. Reményeink szerint a genetikai vizsgálatokkal későbbi, új, oki terápiás eljárások kialakulását is elősegíthetjük.

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European recurrent missense mutation in a Hungarian pedigree with Papillon-Lefèvre syndrome

Papillon–Lefèvre syndrome, a rare disease with autosomal recessive inheritance, is characterized by aggressive periodontitis and palmoplantar hyperkeratosis. Mutations of the cathepsin C gene are responsible for the development of the disease. In this study, we aimed to describe in details the clinical symptoms and to determine the underlying genetic abnormality in two Hungarian siblings affected by Papillon–Lefèvre syndrome. The siblings are under regular dental and dermatological care since their symptoms appeared, but, due to the fact that genetic analysis of Papillon-Lefèvre syndrome has been available for one or two years in Hungary, their mutation screenings were just recently performed. We have identified a homozygous missense mutation on the cathepsin C gene, which is an already published mutation and was originally reported from Germany. Our investigations would like to draw attention to a rare disease, Papillon-Lefèvre syndrome, in which first symptom can be the aggressive periodontitis, and in which genetic testing and for helping childbearing and family planning is now available.

Key words: Papillon–Lefèvre syndrome, cathepsin C gene, aggressive periodontitis, palmoplantar keratoderma, mutation